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THE UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON NORPATCHOULENOL AND STROPHANTHIDIN.

BY

©

MILAN RALITSCH

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND
RESEARCH IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF DOCTOR OF
PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1988

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

SYNTHETIC STUDIES ON NORPATCHOULENOL AND STROPHANTHIDIN.

submitted by MILAN RALITSCH in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

Supervisor
H. J. Liu

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O. Hindsgaul

J. Takats

E. V. Blackburn

External Examiner
D. Gravel

Date: September 29, 1988.

To my parents and sister

and

to the late José Calzada, for initiating me in Organic Chemistry.

Abstract

The first chapter of this thesis describes the first total synthesis of (+)-norpatchoulenol (**15**), the substance responsible for the odor of patchouli oil. Compound **89** was prepared from 10-camphorsulfonic acid (**78**) in 6 steps. Protection of the ketone in **89**, followed by conversion of the ester group into an aldehyde, Wittig reaction and hydrolysis-cyclization produced the key intermediate **101**. Baeyer-Villiger oxidation of **101** followed by hydrolysis of the resulting acetate, oxidation, vinyllithium addition and protection gave rise to the two epimeric keto-ethers **112** and **113**. Treatment of **112** with sodium metal in refluxing tetrahydrofuran produced norpatchoulenol (**15**), along with the tricyclic compounds **117** and **118**. When **113** was subjected to similar conditions, **15**, **119** and **120** were isolated. The direct cyclization of **101** to form the desired tricyclic skeleton has also been investigated. Treatment of **101** with lithium diisopropylamide at low temperature afforded the hydroxy-ketone **76**. The conversion of this compound into norpatchoulenol is currently under investigation. An alternate route to the aldehyde **108** was explored, involving a novel use of a Wittig reagent as a trapping agent. For this, compound **89** was treated with **124** and potassium hydride in dimethyl sulfoxide, to give enol-ether **123**. Hydrolysis of **123** produced the desired aldehyde **108** and its epimer **129**.

In the second chapter, studies towards the synthesis of strophanthidin (**135**) are described. A very efficient synthesis of the dienes **161** and **163** has been developed, involving the photocycloaddition reaction of vinyl acetate with the enone-ester **167**. Diels-Alder reaction of the diene **161** with **150** gave a 1:1:1 mixture of adducts **174**. Similar treatment of **163** produced a 1:1:0.3 mixture of the adducts. Replacing the acetyl group in **163** with a pivaloyl group increased the selectivity of the reaction, leading to the isolation of a 1:1 mixture of adducts **180** and **181**.

Acknowledgements

It is a privilege for the author to express his most sincere gratitude to Prof. H. J. Liu for his outstanding guidance and support during the course of this work and for his interest and assistance in the preparation of this thesis.

The author would also like to thank Eugenio Alvarado and Daniel Figueroa for their help and support. Very special thanks to Angelina Morales, for her unconditional friendship and invaluable encouragement, even in those difficult days.

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Chapter 1

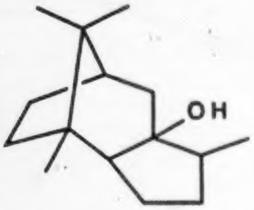
Total Synthesis of Norpatchoulenol

Introduction

Patchouli oil is an essential oil obtained by steam distillation from the dried leaves of an East Indian shrub. Several species of the Labiatae family grow in tropical regions, but only one, *Pogostemon patchouli* Pellet var. suavis Hook (syn. *P. cablin* Benth., *P. heyneanus* Wall) is utilized for the commercial acquisition of the essential oil. This extract has been used as raw material in the perfume industry for over one hundred years. The first notice of its appearance in European commerce seems to have been given by Virey in 1826.[1,2]

The major component of this oil was isolated for the first time by Gal[3] in 1869 and was known for a long time as "patchouli camphor", due to its crystalline appearance, similar to that of camphor. In 1877 Montgolfier[4] established the correct molecular formula for this substance as $C_{15}H_{26}O$. Seventeen years later, in 1894, Wallach[5], suggested that it should be named "patchouli alcohol", the term by which it has been referred to ever since. In 1912 Semmler and Mayer[6] reported the first substantially correct physical constants and proposed a tricyclic structure.

However, it was not until 1949 that Treibs[7] proposed structure **1** and, in 1956, Büchi[8] suggested structure **2**, both of which were later shown to be incorrect.



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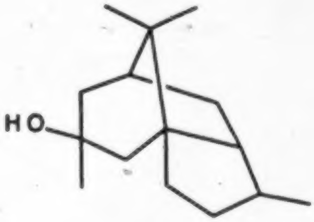
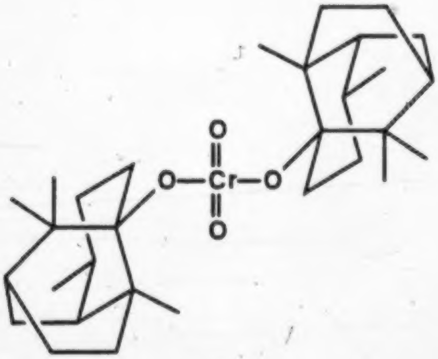


2

Finally, in 1963, Büchi and coworkers[9] isolated a pure crystalline chromate ester of patchouli alcohol (or, more recently, patchoulol) and were able to determine its structure (**3**) unequivocally by X-ray crystallographic analysis. This led to the accurate structure of the natural product, as depicted in **4**.



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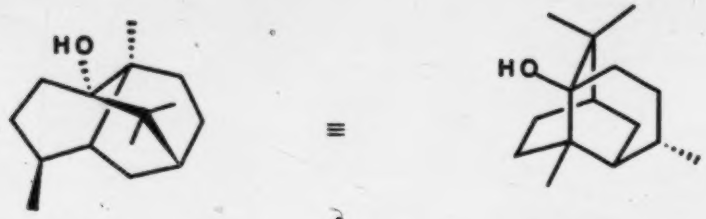

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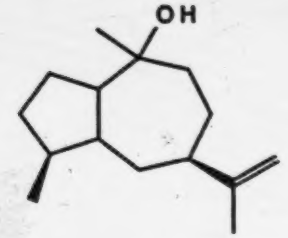
Patchouli alcohol, however, accounts for only 35 to 40% of the substances contained in the essential oil. To 1966 ten compounds, other than patchoulol, had been isolated from patchouli oil and characterized. These are: pogostol (**5**), α-patchoulene (**6**), β-patchoulene (**7**), seychellene (**8**), α-gaiene (**9**), caryophyllene (**10**), β-elemene (**11**) and three sesquiterpenic alkaloids, patchoulipyridine (**12**), epigaiapyridine (**13**) and gaiapyridine (**14**).

None of these compounds exhibit the characteristic odor of patchouli oil. Much to the contrary, the absence of some of them, specifically the alkaloidal components, enhances the aroma. Thus, the oil washed with an aqueous acidic solution and subsequently neutralized has an odor noticeably more appreciated by perfumers than the crude oil.

In 1973, Teisseire *et al.* reported the isolation of the substance responsible for the scent of patchouli oil.[10,11] The same authors elucidated, shortly thereafter,[12,13] the structure of said substance



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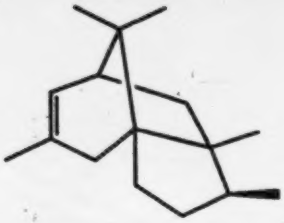

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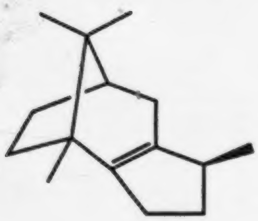

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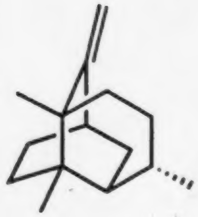

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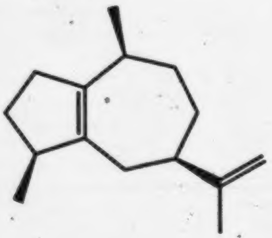

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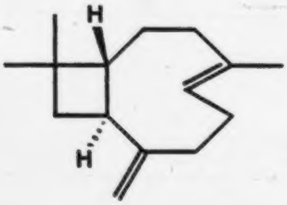

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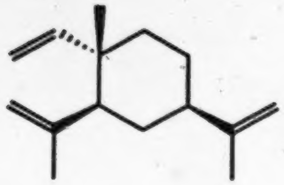

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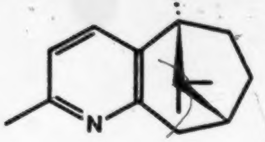

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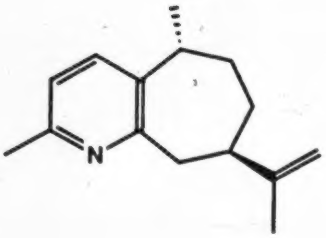

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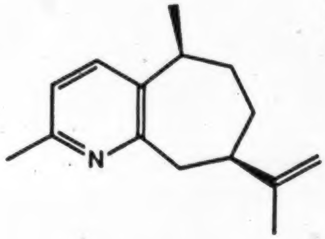

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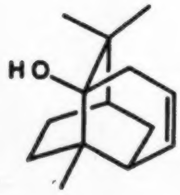

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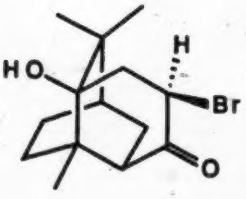


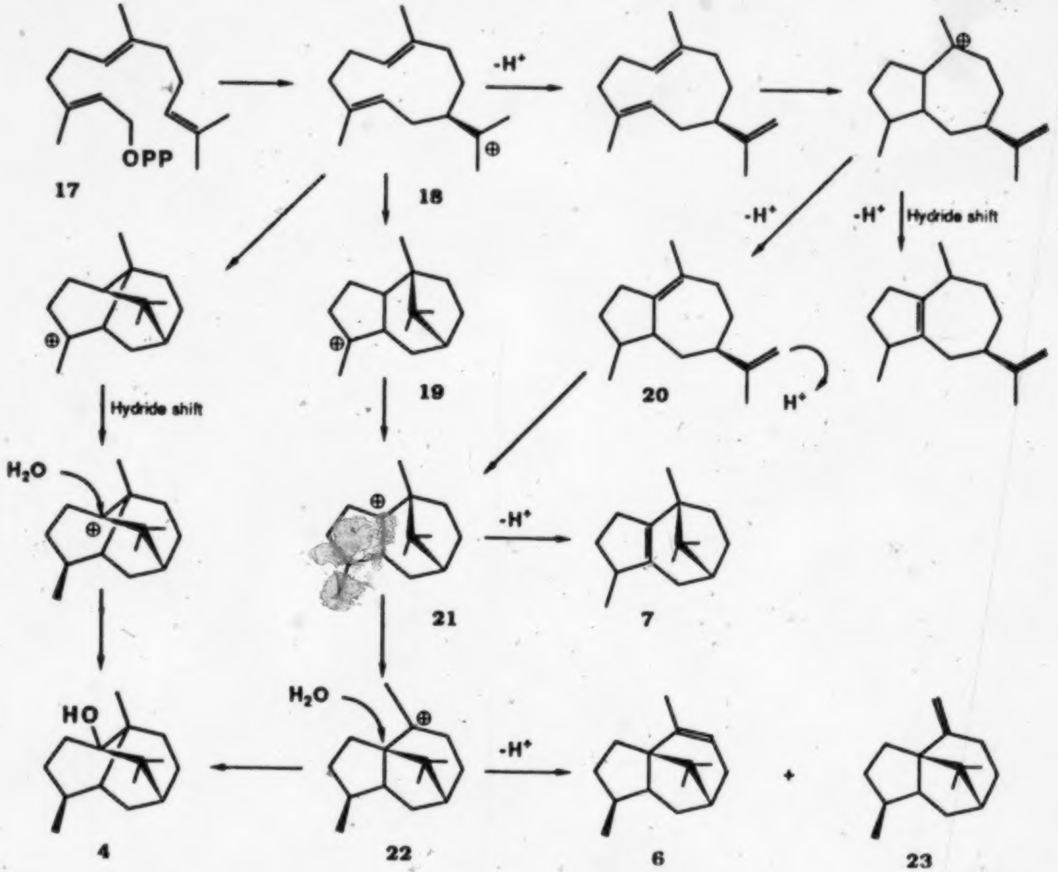
16

and named it "norpatchoulenol" (**15**). The structural determination of this compound was carried out by means of extensive and careful chemical degradation, combined with spectroscopic analysis. The accuracy of the structure was later confirmed[14] by X-ray crystallographic analysis of the bromo derivative **16**.

As a sesquiterpene, patchouli alcohol is biosynthetically derived from *trans, trans*-farnesyl pyrophosphate (**17**)[15,16] (Scheme 1). A number of researchers have proposed[17-19] that the process involves the protonation of the isopropenyl group of an α-bulnesene intermediate (**20**), followed by cyclization and a series of Wagner-Meerwein rearrangements (**20**→**21**→**22**→**4**).

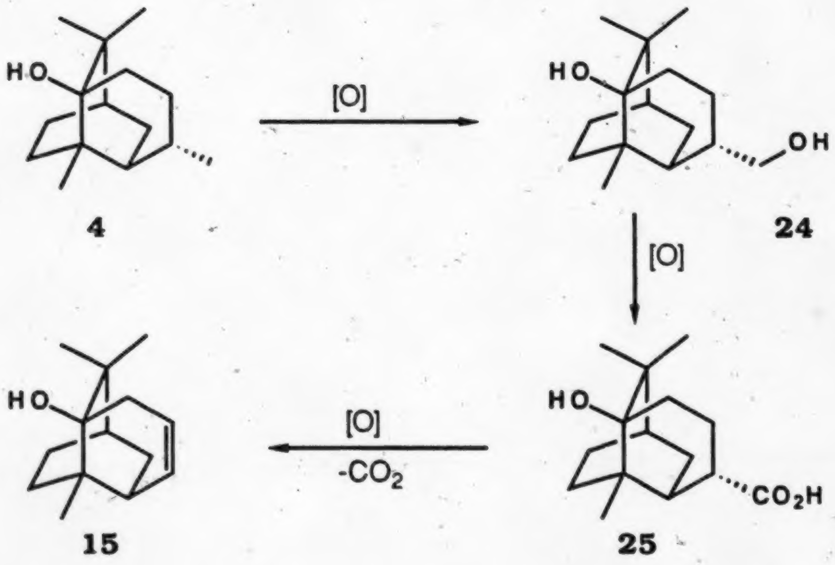
More recently, Croteau[20] has reexamined the biogenetic possibilities and proposed an alternate pathway without the protonation-deprotonation steps. Rather, it involves only tertiary cation intermediates and a 1,3-hydride shift to yield carbocation **21**, from which the patchoulenes (**6**, **7** and **23**) and patchouli alcohol (**4**) would ultimately arise (i. e., **17**→**18**→**19**→**21**). This suggestion is supported by the results of a number of experiments, such as *in vivo* incorporation of [12,13-^{14}C;1-^{3}H]farnesyl pyrophosphate and [12,13-^{14}C;6-^{3}H]farnesyl pyrophosphate using a cell free enzymatic system prepared from *P. cablin* leaves.

Scheme 1


OPP
17
-H⁺
18
-H⁺
-H⁺
Hydride shift
Hydride shift
19
20
H⁺
H₂O
-H⁺
21
7
HO
H₂O
-H⁺
4
22
6
+
23

Norpatchoulenol in turn is considered to be biogenetically derived from patchouli alcohol. In 1975 Ourisson and coworkers[21] carried out an administration experiment of patchouli alcohol to rabbits and isolated two biooxidation products: hydroxy patchouli alcohol (**24**) and the corresponding carboxylic acid (**25**). Based on this result they proposed a biosynthetic pathway involving several oxidation steps and a decarboxylation (Scheme 2).

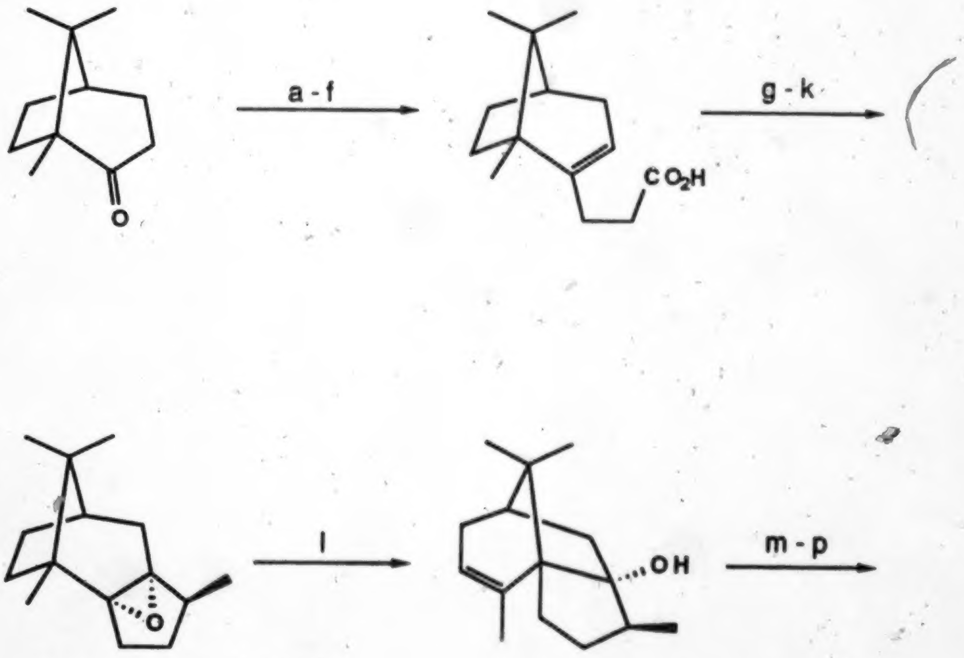
Scheme 2



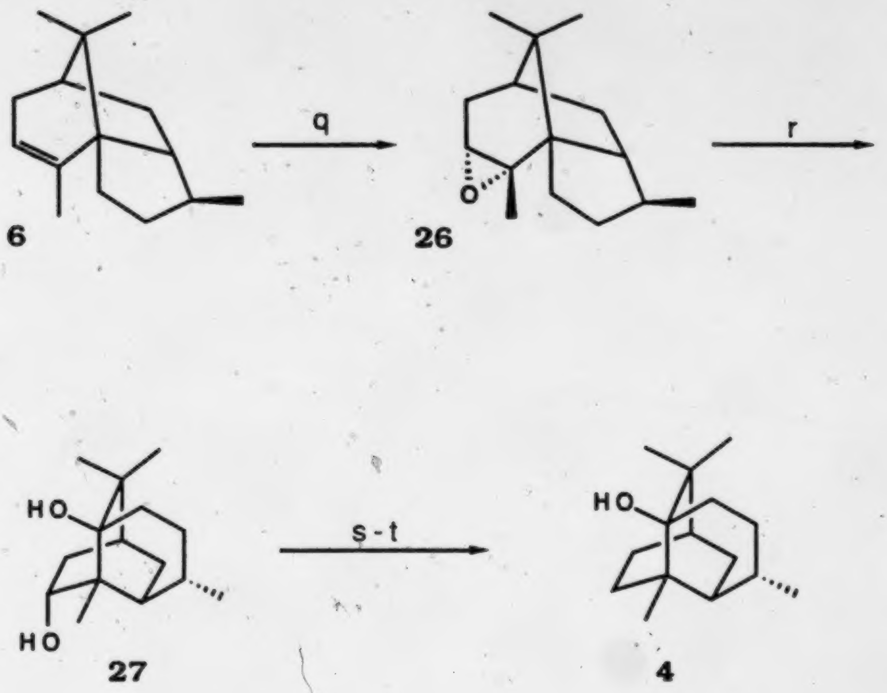
To this date, there have been six total syntheses of patchouli alcohol. Five of these approaches produced the racemic material and the other involved the preparation of both (-)-patchouli alcohol, the natural product, and its dextrorotatory enantiomer by identical routes from separate, commercially available, enantiomeric starting materials. In addition, two total syntheses of racemic norpatchoulenol and one of the unnatural (-)-isomer have appeared in the literature.

The first synthesis of patchouli alcohol was reported by Büchi and coworkers in 1964[22,23] (Scheme 3). It is interesting to note that at that point of time **2** was considered to be the correct structure for the naturally occuring compound and all efforts were directed towards the preparation of this compound.

Scheme 3

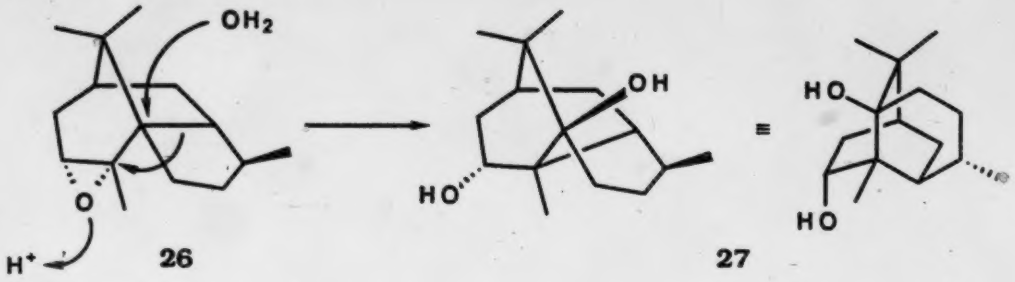


Scheme 3 (cont.)

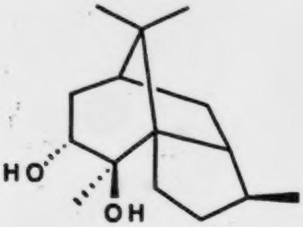


(a) CH_2=$CHCH_2MgCl$; (b) 1)B_2H_6; 2)H_2O_2; (c) Ac_2O; (d) $POCl_3$, Pyridine; (e) LAH; (f) CrO_3; (g) $SOCl_2$; (h) $AlCl_3$, CS_2; (i) Ph_3P=CH_2; (j) H_2, Raney-nickel; (k) CH_3CO_3H; (l) $BF_3 \cdot OEt_2$; (m) 1)B_2H_6, 2)H_2O_2; (n) Ac_2O, Pyridine, reflux; (o) H_2, Raney-nickel; (p) pyrolysis, 350°; (q) CH_3CO_3H; (r)$BF_3 \cdot OEt_2$; (s) CrO_3; (t) $H_2N\text{-}NH_2 \cdot H_2O$, KOH.

Thus, the sequence of reactions originally conceived involved the oxidation of α-patchoulene (**6**) to epoxide **26**, which was then hydrolyzed to a diol, at that moment thought to be **28**. Isolation of the final product was accomplished by treatment of the diol with chromium trioxide followed by a Wolff-Kishner reduction of the resulting hydroxy-ketone. It was only thanks to a fortuitous rearrangement of epoxide **26** (**26→27**) that the authors were able to obtain the desired material **4**.



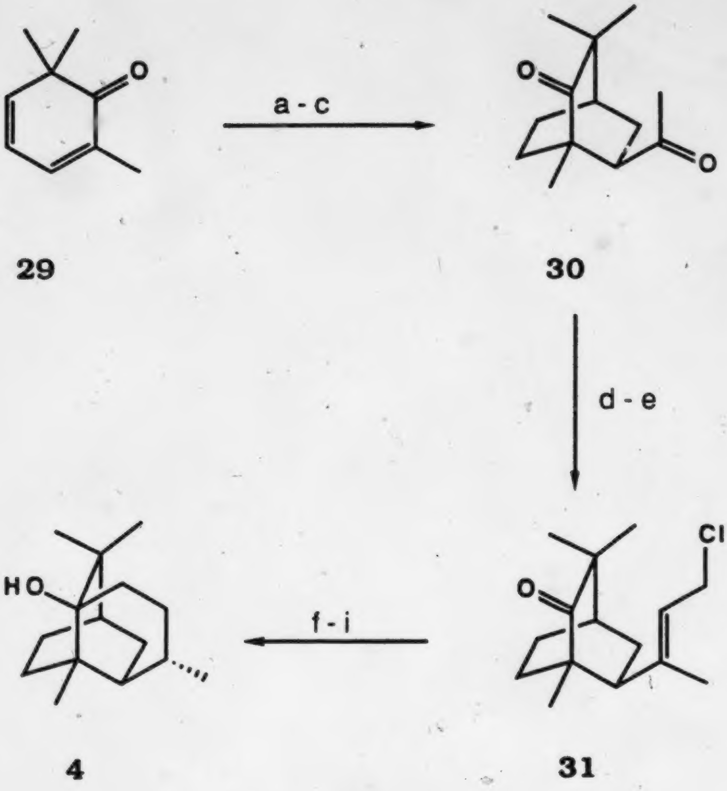
26 **27**



28

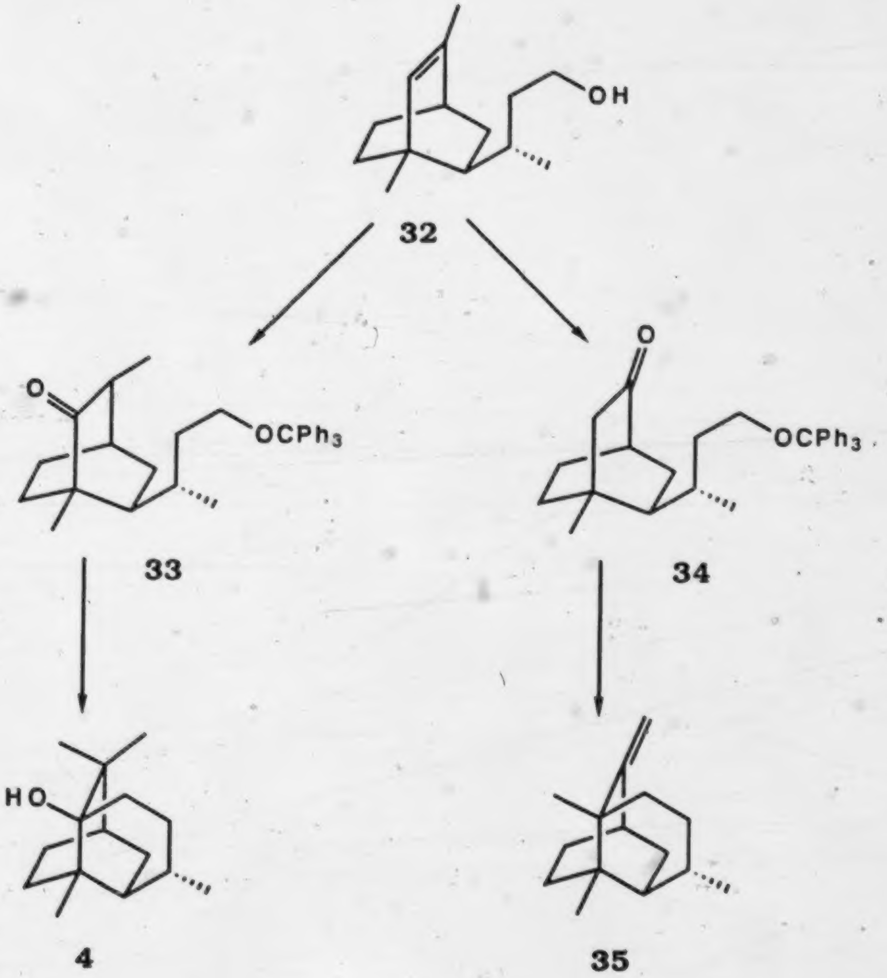
In 1968 Danishefsky and Dumas[24] used the Diels-Alder reaction of dienone **29** with methyl vinyl ketone to form the bicyclo[2.2.2]octane system of diketone **30** and then a key intramolecular reductive cyclization of the bromide derived from **31** to produce the tricyclo[5.3.1.$0^{3,8}$]undecane (homoisotwistane) skeleton of patchoulol (Scheme 4). These authors also reported the synthesis of 4-*epi*-patchouli alcohol, unknown from natural sources.

Scheme 4

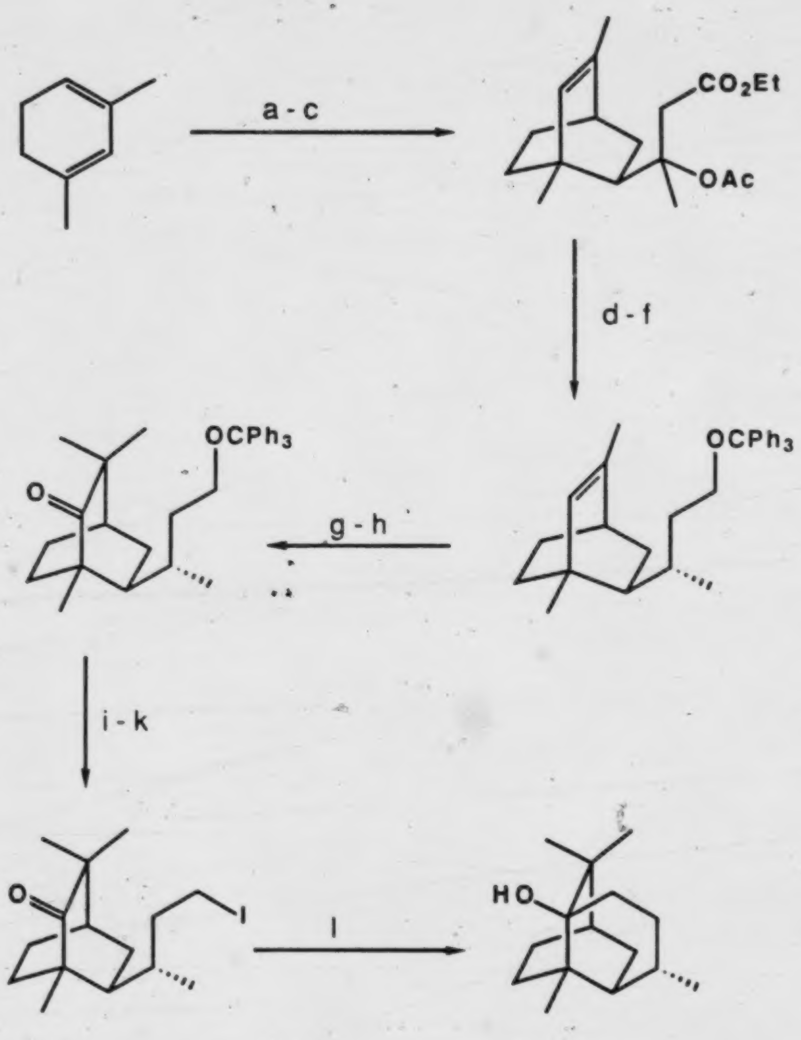


(a) MVK; (b) H_2, Pd/C; (c) $NaOCH_3$, CH_3OH; (d) vinyllithium, THF; (e) HCl, $CHCl_3$; (f) H_2O, dioxane; (g) H_2, Pd/C, EtOAc; (h) PBr_3; (i) Na, THF, reflux.

Mirrington and Schmalzl[25] made use of a similar approach in a more efficient manner (Scheme 5). By delaying the introduction of the carbonyl group until after the bicyclic system was formed, it was possible to synthesize both patchouli alcohol (**32**→**33**→**4**) and seychellene (**32**→**34**→**35**) from the common intermediate **32**.


OH
32
O
OCPh3
33
O
OCPh3
34
HO
4
35

Scheme 5

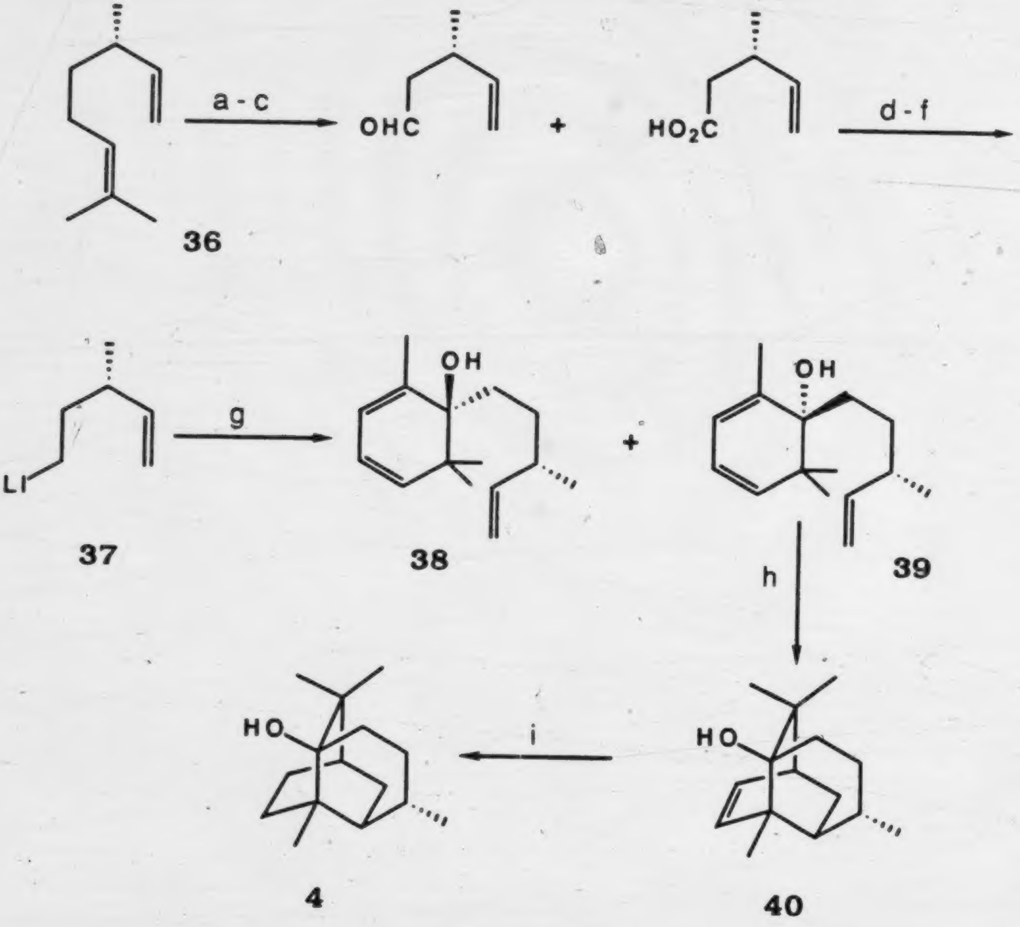

a - c
CO_2Et
OAc
d - f
OCPh$_3$
O
OCPh$_3$
g - h
i - k
O
I
l
HO

4

(a) MVK; (b) $BrCH_2CO_2Et$, Zn, benzene, reflux; (c) $PhNMe_2$, CH_3COCl; (d) NaOEt, EtOH; (e) Li/NH_3(l), EtOH; (f) Ph_3CCl, pyridine, benzene, reflux; (g) 1)B_2H_6, THF; 2)CrO_3, pyridine; (h) 1)$Ph_3C^-K^+$; 2) CH_3I; (i) H_2, Pd/C, EtOH; (j) TsCl, pyridine; (k) NaI, acetone; (l) Na, THF, 100°, sealed tube.

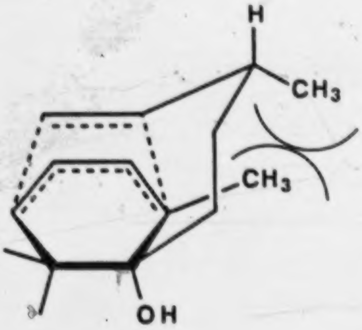
The first synthesis of optically active patchouli alcohol was carried out by Näf and coworkers[26,27] (Scheme 6).

Scheme 6


a - c
OHC
+
HO_2C
d - f
36
Li
g
OH
+
OH
37
38
39
h
HO
i
HO
4
40

(a) CH_3CO_3H, NaOAc, CH_2Cl_2, 0°; (b) $LiClO_4$, hexane, reflux; (c) KOt-Bu, O_2, glyme, 20°; (d) LAH, Et_2O; (e) PBr_3, pyridine; (f) Li, Et_2O, -8°; (g) 2,6,6-trimethyl-2,4-cyclohexadiene-1-one, Et_2O, -60°; (h) xylene, KOt-Bu, 280°, sealed tube; (i) H_2, PtO_2, EtOH.

The chiral lithium salt **37** was prepared from the commercially available (-)-3,7-dimethyl-1,6-octadiene (**36**). Treatment of **37** with 2,6,6-trimethyl-2,4-cyclohexadien-1-one in ether at -60°C afforded a diastereoisomeric mixture of trienols **38** and **39**. Compound **39** underwent intramolecular Diels-Alder cyclization in the presence of potassium tertiary butoxide to produce the tricyclic enol **40**, which was subsequently reduced to (-)-patchoulol. Interestingly, compound **38** did not undergo the Diels-Alder reaction. The diastereoselectivity is accounted for by the presence of severe 1,3-diaxial interactions in the transition state **41**, disfavoring the formation of the precursor of *epi*-patchouli alcohol.



41

(+)-Patchouli alcohol, the enantiomer of the naturally occurring substance, was similarly prepared from the antipode of compound **36**, which is also commercially available.

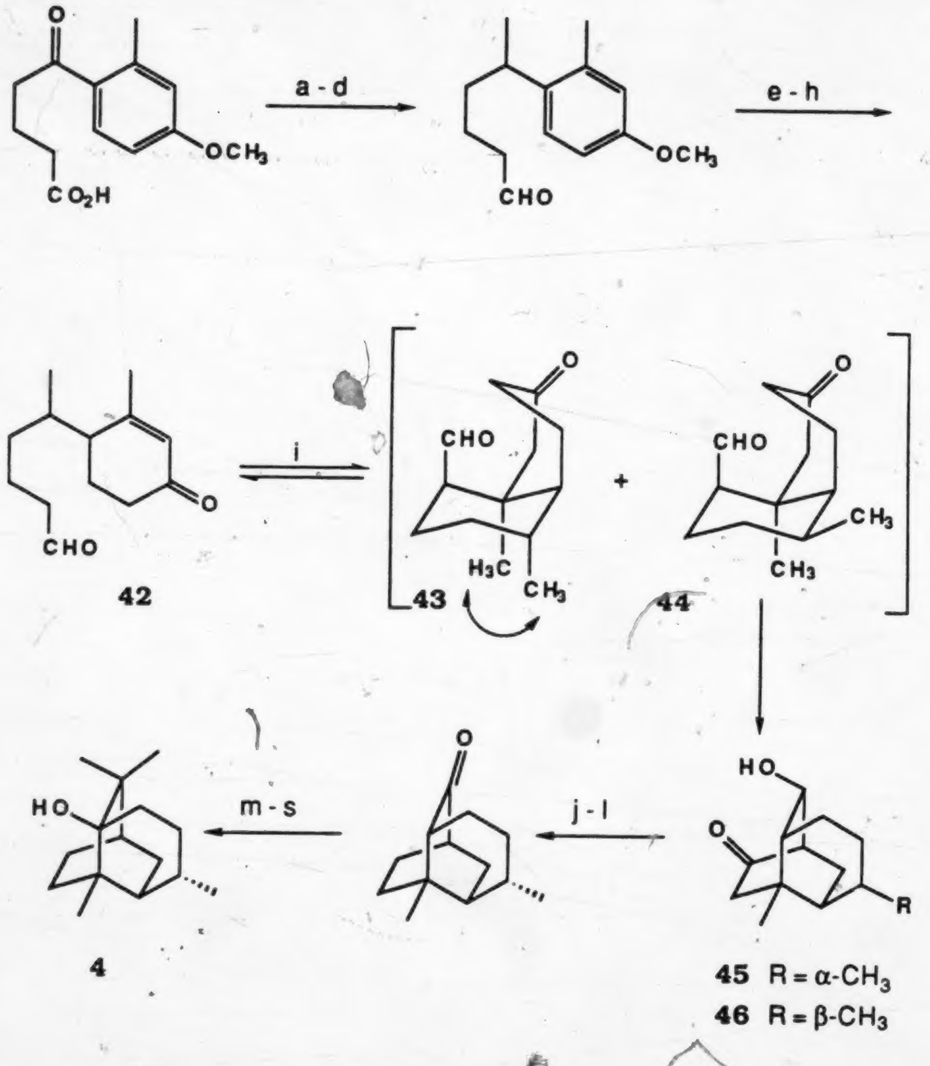
Yamada and collaborators[28] utilized an elegant double cyclization reaction as the key step for their approach. Thus, the unsaturated keto-aldehyde **42** (Scheme 7) experienced intramolecular Michael addition under the action of potassium tertiary butoxide to give a mixture of diastereomeric *cis*-decalones. In the second stage of the cyclization **43** and **44**, which necessarily assume the conformation shown in the scheme for intramolecular aldol condensation, would yield the tricyclic ketol **45** and its epimer **46**. The fact that compound **46** was only observed as a minor product was explained by the authors on the basis of a 1,3-diaxial interaction in the transition state from **43** to **46**, as indicated by the arrows, which inhibits the formation of **46**. In contrast, no such unfavorable steric factor is present in going from **44** to **45**. However, no proof was presented that **43** was actually formed in significant amount and the researchers might have overlooked the possibility that the outcome of the reaction may be governed by the Michael addition process, rather than by the second stage of the cyclization. That is, if **43** is formed in small amount then **46** will also be produced in small quantity.

The last preparation of patchoulol found in the literature to this date has been described by Teisseire and coworkers[29] in 1980. These authors use the same approach as Danishefsky,[24] with minor modifications towards the end of the synthesis (Scheme 8).

In 1983 the same authors published[30] some further insight into their approach. The reductive cyclization of the unsaturated methoxymethyl ether **47** gives, in addition to patchouli alcohol, a small amount of the epimeric hydroxy-ethers **49**. These compounds arise from a five-membered ring cyclization of the intermediate radical-anion **48**.

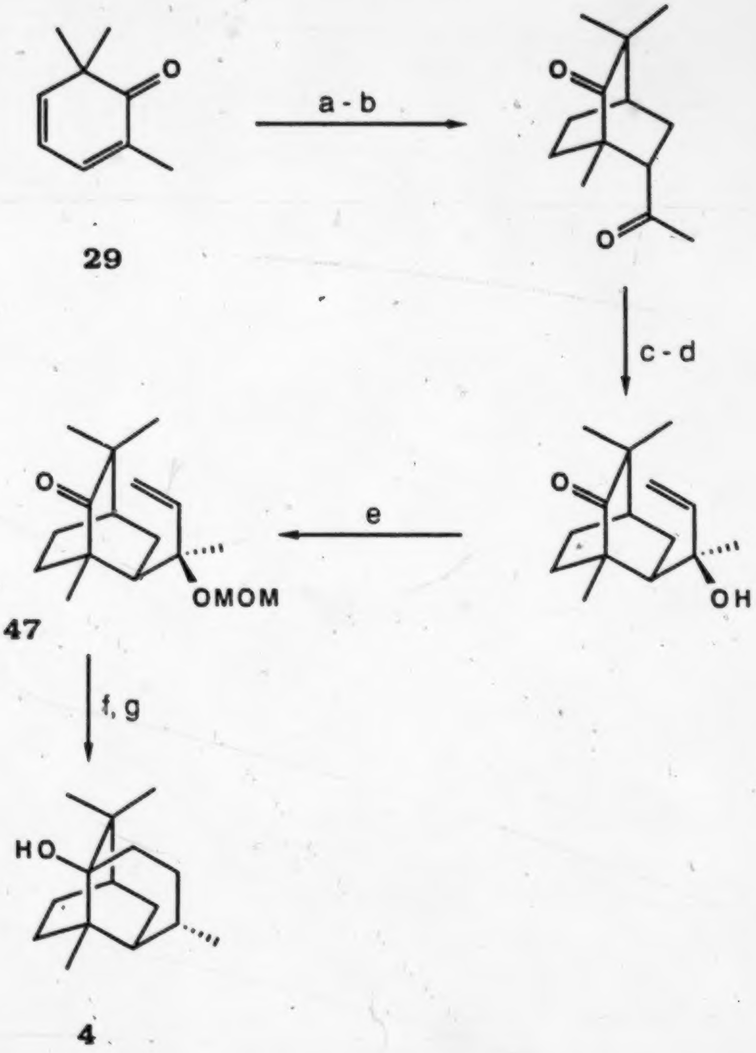
Furthermore, exposure of **50**, an epimer of **47**, to the same reaction conditions afforded the five-membered cyclization products **51** exclusively.

Scheme 7

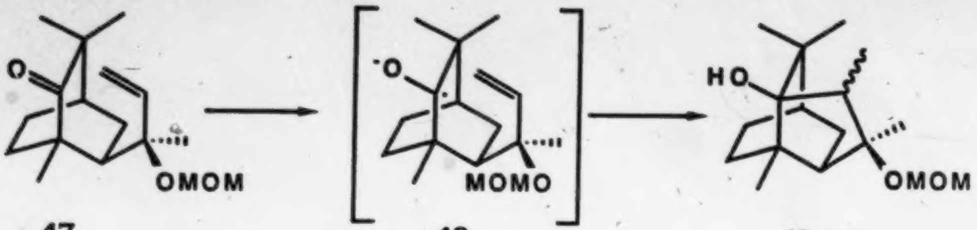

O
OCH3
CO2H
a - d
OCH3
CHO
e - h
CHO
O
42
i
CHO
O
H3C
CH3
43
+
CHO
O
CH3
CH3
44
HO
O
R
45 R = α-CH3
46 R = β-CH3
j - l
O
m - s
HO
4

(a) $Ph_3P{=}CH_2$, DME, DMSO, -30°→r.t.; (b) H_2, Pd/C, EtOH; (c) LAH, Et_2O, 0°; (d) PCC, CH_2Cl_2; (e) PTSA, $(CH_2OH)_2$, toluene, reflux; (f) 1) Li/NH_3(l), THF, t-BuOH, -33°; 2) oxalic acid, CH_3OH, H_2O; (g) $NaOCH_3$, CH_3OH; (h) AcOH, H_2O; (i) KOt-Bu, t-BuOH; (j) $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$; (k)Raney-nickel, EtOH; (l) CrO_3, pyridine; (m) 1)LDA, THF; 2)$MoO_5{\cdot}Py{\cdot}HMPA$; (n) 1)NaH; 2)$CH_3I$; (o) CH_3Li; Et_2O; (p) $SOCl_2$, pyridine, benzene; (q) bis(N-a-phenethylsalicylaldimidato)Cu(II), CH_2N_2, hexane-benzene; (r) H_2, PtO_2, AcOH, NaOAc; (s) CrO_3, AcOH, CH_2Cl_2.

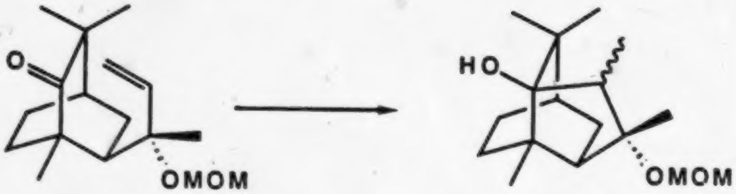
Scheme 8


O
29
a - b
O
O
c - d
O
OMOM
47
e
O
OH
f, g
HO
4

(a) MVK, benzene, reflux; (b) H_2, Pd/C, pentane; (c) $NaOCH_3$, CH_3OH; (d) vinyllithium, THF, -20°; (e) $(CH_3OCH_2)Et_3N^+Cl^-$, CH_3CN, reflux; (f) Na, THF, reflux; (g) H_2, Pd/C, EtOH.

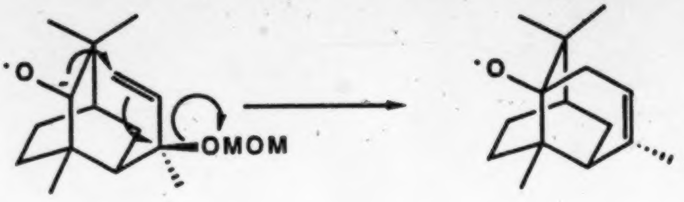


47 **48** **49**



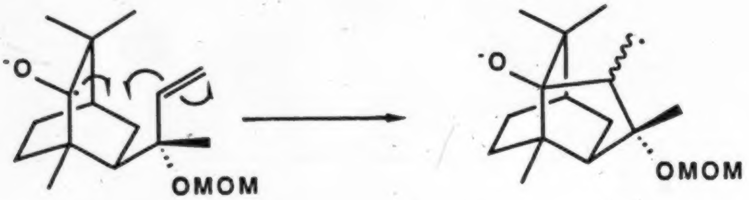
50 **51**

The formation of these byproducts is not surprising, since they arise from a favorable 5-*Exo-Trig*[31] ring closure. The formation of patchouli alcohol in contrast, follows a 6-*Endo-Trig* process, known to be a less preferred pathway. The mechanisms proposed for the two reactions are somewhat different. The six-membered ring cyclization is considered to follow an internal displacement (S_CN' mechanism[32]), where the ketyl radical anion in **52** acts as a nucleophile and the allylic methoxymethyl ether as the leaving group.



52

On the other hand, the five-membered ring product is formed by means of a radical cyclization of the ketyl in intermediate **53** onto the double bond.



53

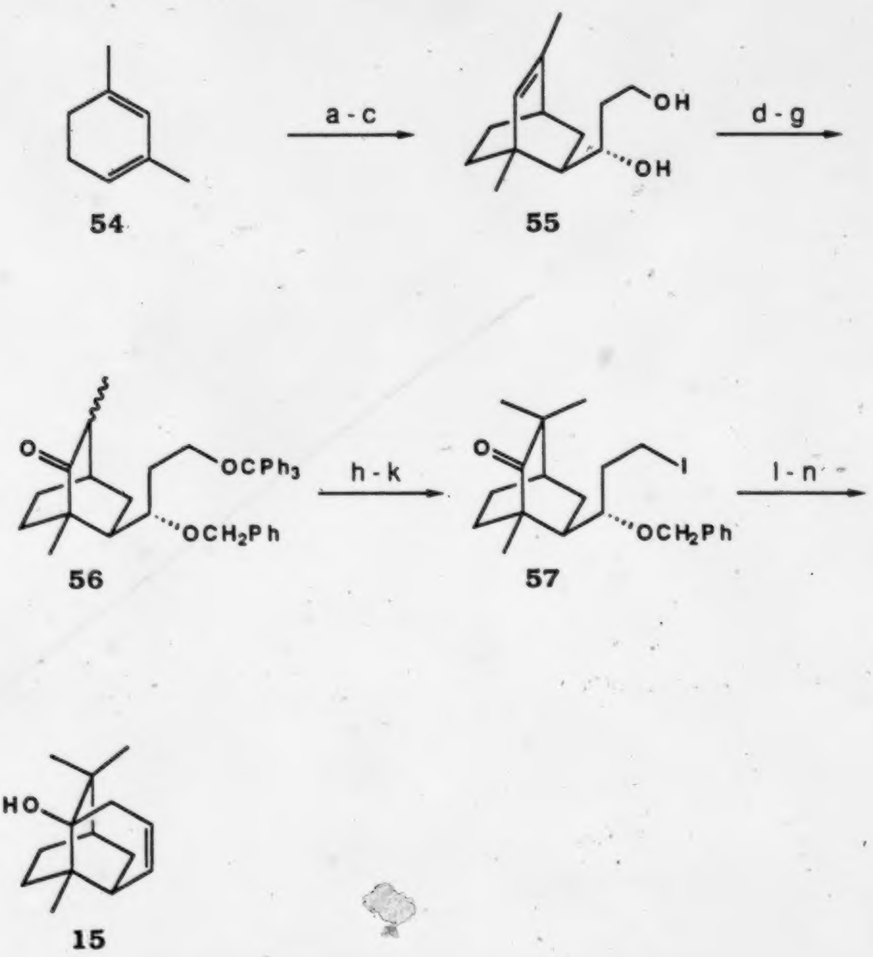
To explain the difference in the outcome of the reactions of **47** and **50** the authors propose that the displacement process takes place in a suprafacial fashion. That is, the nucleophile attacks *syn* to the leaving group. This geometry is allegedly allowed in the case of **47**, but impossible for **50**. However, this is not evident from careful examination of models of such compounds. Furthermore, the literature presents contradictory arguments as to the stereochemical course of the intramolecular displacement reactions, with examples of both *anti* and *syn* relationships.[32-35]

In the case of norpatchoulenol, five syntheses have been reported. Three of them have been carried out by the same research group and involve similar methodology. One of these three approaches produces (-)-norpatchoulenol, the unnatural isomer.

The first synthesis was published by Teisseire *et al.* in 1974[36] (Scheme 9). It involves an adaptation of the pathway used by Danishefsky[24] and Mirrington[25] for the preparation of patchouli alcohol. Diels-Alder reaction of diene **54** with acrolein followed by a Reformatsky reaction and reduction gave diol **55**. After selective protection of the hydroxy groups, a hydroboration-oxidation sequence produced compound **56**. Methylation followed by a three-step replacement of the trityloxy group by iodide gave **57**, which was then subjected to reductive cyclization, cleavage of the benzyl protecting group and dehydration to afford the desired product **15**.

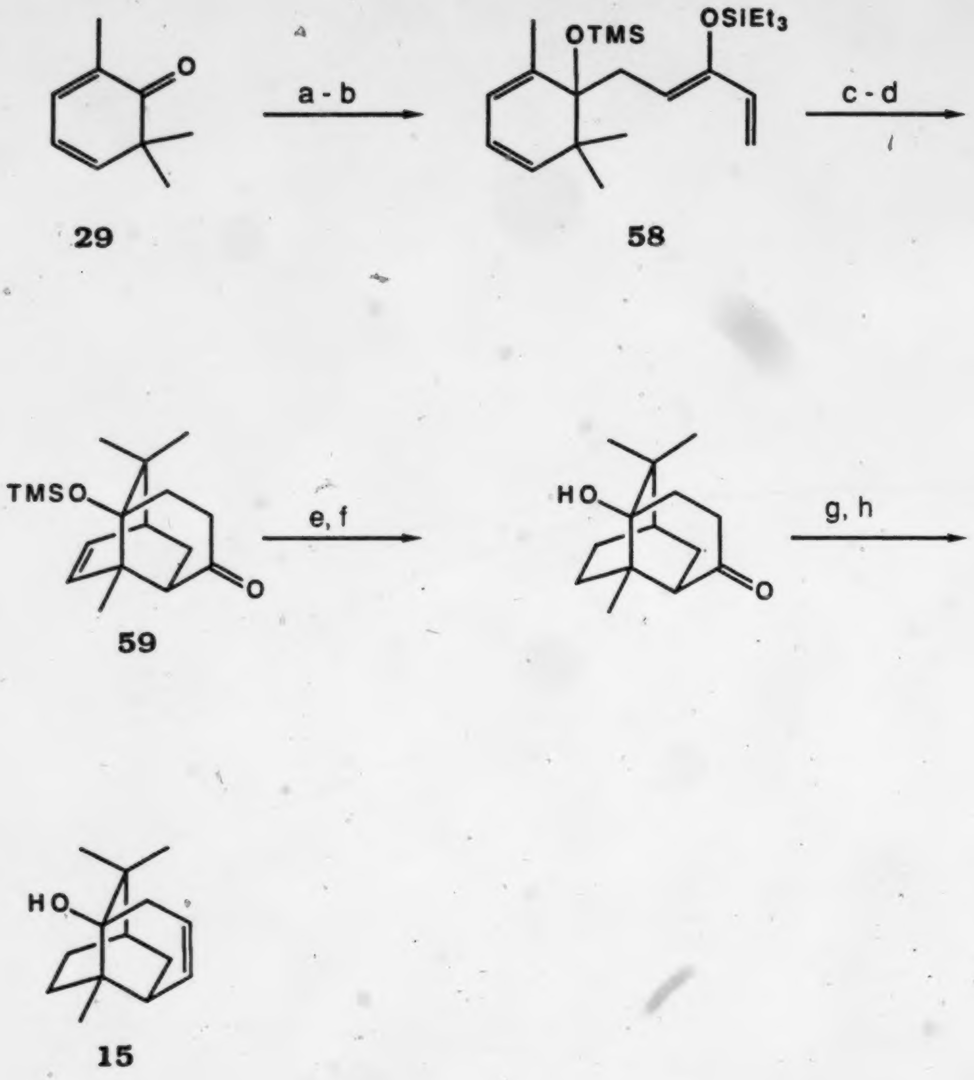
In 1978 Oppolzer and Snowden[37] reported an approach to norpatchoulenol using a strategy similar to the one utilized by Näf[26,27] to produce patchoulol (Scheme 10). Reaction of divinyltriethylsilyloxymethane lithium with dienone **38** followed by protection of the resultant tertiary alcohol with a trimethylsilyl group gave compound **58**. Selective deprotection and intramolecular Diels-Alder reaction afforded **59**, which was then hydrolyzed, hydrogenated and then subjected to a Bamford-Stevens reaction to finally give norpatchoulenol.

Scheme 9


a - c
d - g
h - k
l - n
OH
OH
OCPh$_3$
OCH$_2$Ph
I
OCH$_2$Ph
O
O
HO
54
55
56
57
15

(a) acrolein, reflux; (b) $BrCH_2CO_2Et$, Zn, $HgCl_2$, benzene; (c) LAH, Et_2O; (d) Ph_3CCl; (e) 1)NaH; 2)$PhCH_2Br$; (f) B_2H_6, THF; (g) CrO_3, pyridine; (h) 1)$Ph_3C^-K^+$; 2) CH_3I; (i)80% aq. AcOH; (j) TsCl, pyridine; (k) NaI, acetone; (l) Na, THF; (m) Li, $EtNH_2$; (n) brosyl chloride, pyridine.

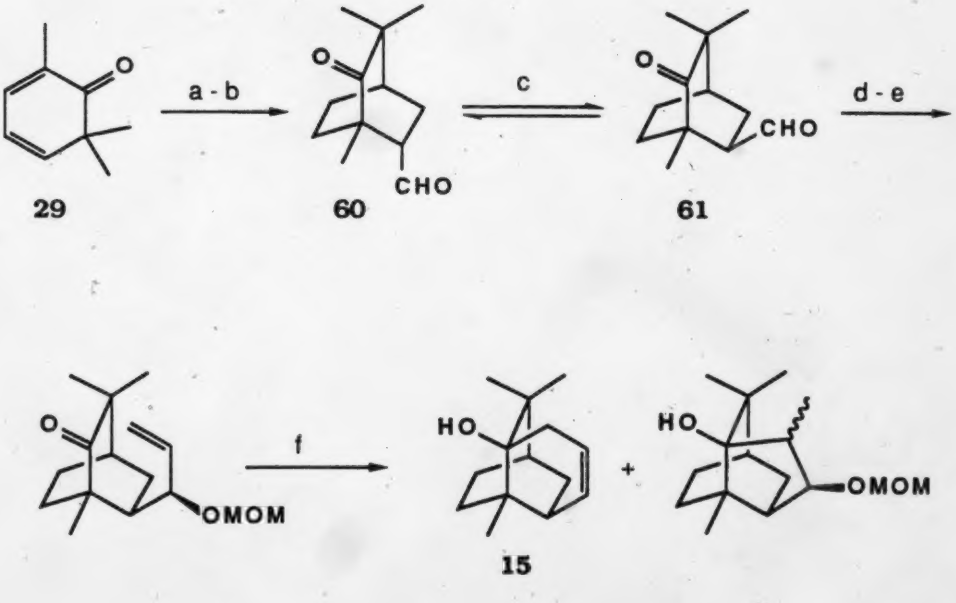
Scheme 10


OTMS
OSiEt3
O
a - b
c - d
29
58
TMSO
O
e, f
HO
O
g, h
59
HO
15

(a) $(CH_2{=}CH)_2C(OSiEt_3)^-Li^+$, THF; (b) TMSCl, THF, HMPT; (c) KF, MeOH; (d) benzene, sealed tube, 230°; (e) AcOH, H_2O, THF; (f) H_2, PtO_2; (g) $TsNHNH_2$, HOAc; (h) CH_3Li, Et_2O.

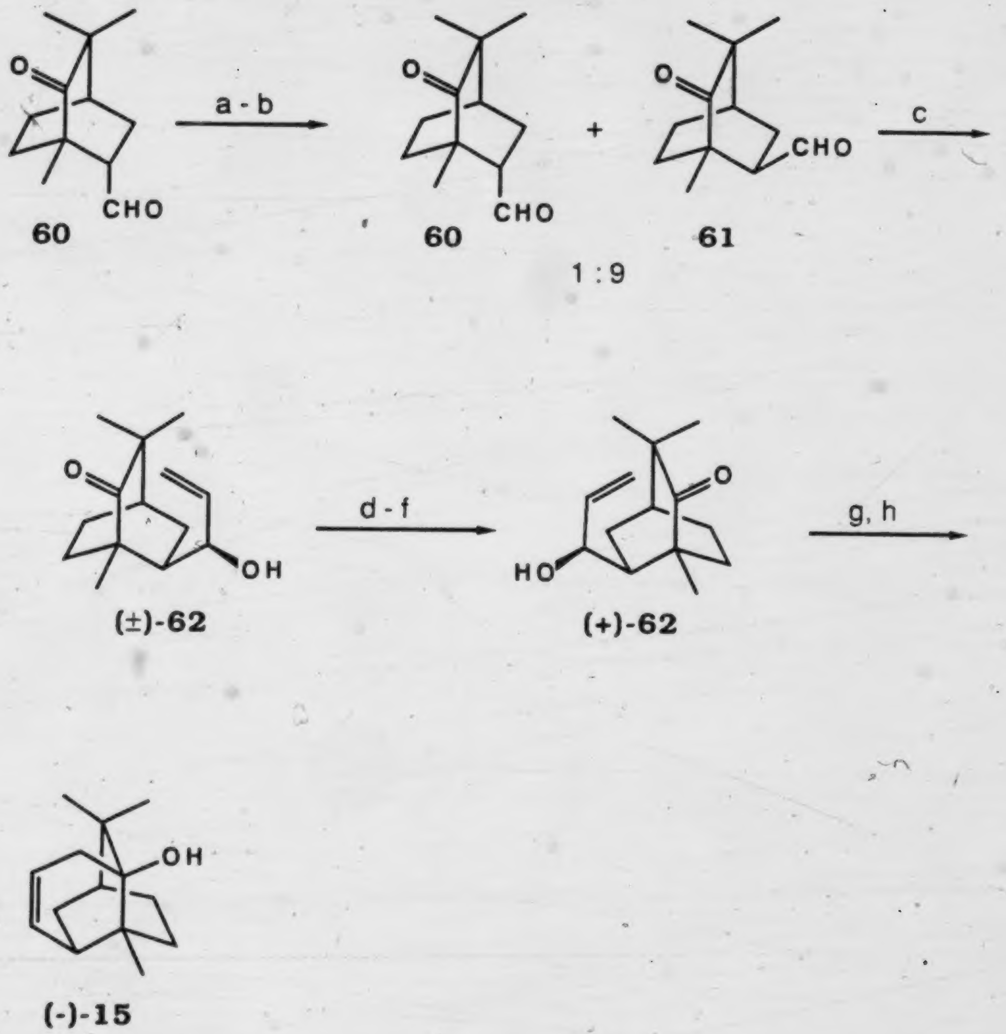
Teisseire contributed yet another synthesis based on the Diels-Alder reaction of 2,6,6-trimethyl-2,5-cyclohexadiene-1-one (**29**) with acrolein[38]. As shown in Scheme 11, a five-membered ring cyclization product is also observed as a secondary product in the last step, in agreement with the results obtained by the same group during the preparation of patchouli alcohol. Further investigation[30] led to some minor modifications (Scheme 12). The epimerization of keto-aldehyde **60** was accomplished more efficiently by means of a deprotonation-protonation sequence.

Scheme 11



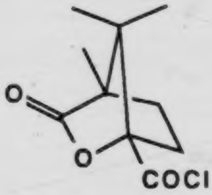
(a) acrolein, reflux; (b) H_2, Pd/C; (c) piperidinium acetate; (d) vinylmagnesium bromide; (e) methoxymethyltriethylammonium chloride, CH_3CN, reflux; (f) Na, THF, reflux.

Scheme 12


O
CHO
60
a - b
O
CHO
60
+
O
CHO
61
1 : 9
c
O
OH
(±)-62
d - f
O
HO
(+)-62
g, h
OH
(-)-15

(a) NaH, THF; (b) H_2O, pH 7; (c) vinylmagnesium bromide, THF; (d) (-)-camphanoyl chloride, pyridine; (e) fractional crystallization; (f) NaOH, H_2O-THF; (g) methoxymethyltriethylammonium chloride; (h) Na, THF, reflux.

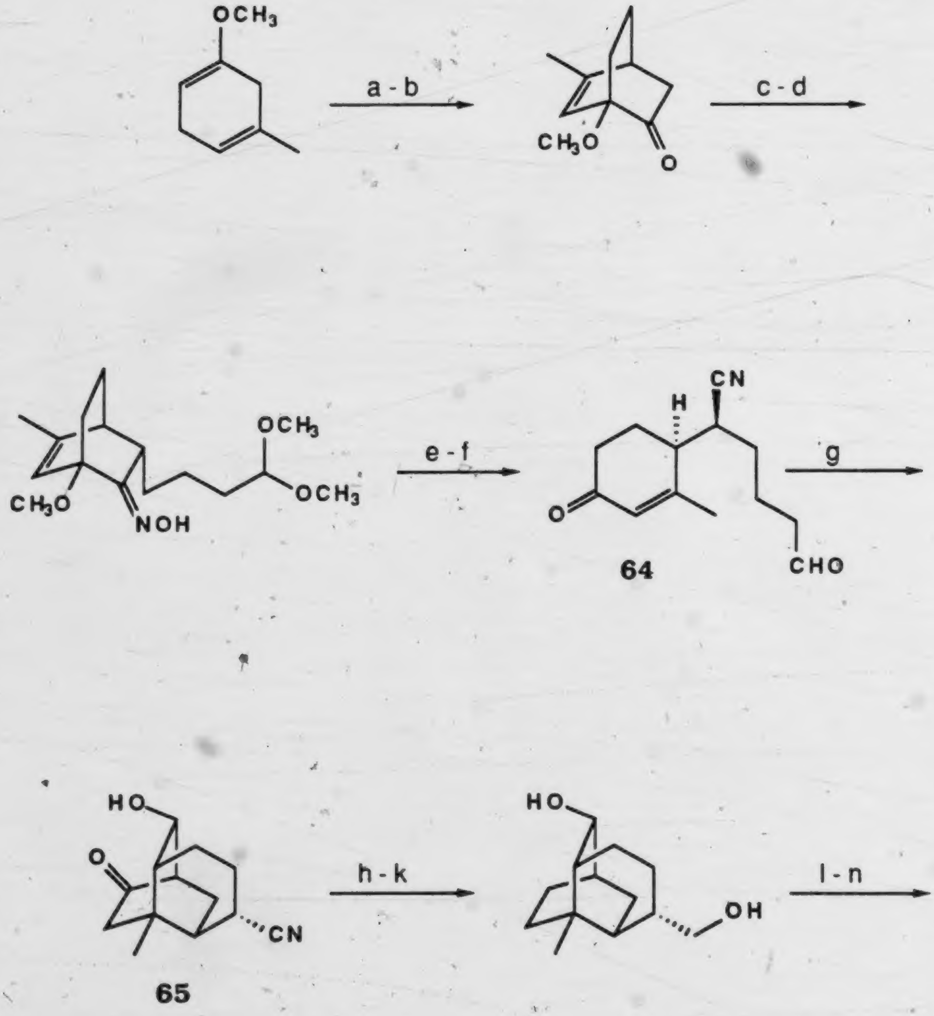
Thus, treatment of **60** with sodium hydride in tetrahydrofuran, followed by a kinetic protonation using a buffer solution at pH 7 gave a 1:9 mixture of **60** and **61**. This is in contrast to the previously found 3:2 ratio when the equilibration was carried out with piperidinium acetate. Furthermore, resolution of the vinyl hydroxyketone **62** was accomplished by fractional crystallization of the two diastereomeric esters obtained by reaction with camphanoyl chloride (**63**). Completion of the synthesis from (+)-**62** resulted in the production of (-)-norpatchoulenol, the unnatural stereoisomer.



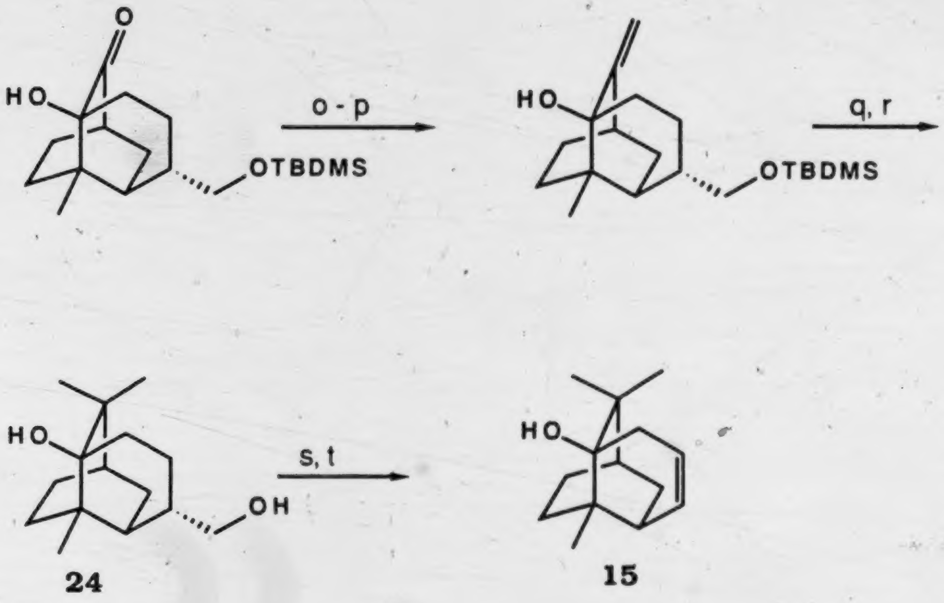
63

Yamada and coworkers[39] realized a lengthy but nevertheless elegant preparation of racemic norpatchoulenol (Scheme 13). As in their synthesis of patchouli alcohol[28], the double cyclization of compound **64** to **65** plays a key role in the process. The final steps were carried out following the biogenetic route: oxidation of hydroxy patchouli alcohol (**24**) to the corresponding carboxylic acid and then oxidative decarboxylation.

Scheme 13


OCH₃
a - b
CH₃O
O
c - d
OCH₃
CH₃O
OCH₃
NOH
e - f
H
CN
O
64
CHO
g
HO
O
CN
65
h - k
HO
OH
l - n

Scheme 13 (cont.)

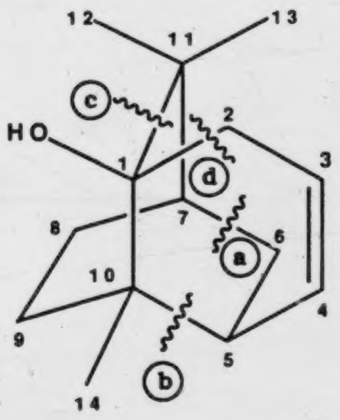


(a) CH_2=CHCN, benzene, reflux; (b) 1) LDA, THF, -78°C; 2) O_2, -78°C; 3) Na_2SO_3, 0°→25°C; (c) 1)LDA; 2)$(CH_3O)_2CH(CH_2)_3I$; (d) $NH_2OH \cdot HCl$, NaOAc, CH_3OH, H_2O, reflux; (e) TsCl, LiCl, pyridine; (f) AcOH, H_2O; (g) Et_2NH, CH_3OH, H_2O, reflux; (h) $(CH_2SH)_2$, $BF_3 \cdot OEt_2$; (i) DIBAL, toluene, CH_2Cl_2, -78°; (j) $NaBH_4$, CH_3OH; (k) Raney-nickel, EtOH, reflux; (l)TBDMSCl, DMAP, TEA, CH_2Cl_2; (m) PCC, CH_2Cl_2; (n) 1)LDA, THF, -78°; 2) $MoO_5 \cdot Py \cdot HMPA$; (o) $PhSO(=NCH_3)CH_2^-Li^+$, THF, 0°; (p) Al(Hg), THF, AcOH, H_2O; (q) 1)CH_2N_2, CuOTf, benzene; 2)PtO_2, H_2, AcOH, NaOAc; (r) Bu_4NF, THF; (s) PDC, DMF; (t) $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine, benzene, H_2O.

As of the time of writing of this thesis no synthesis of the naturally occuring (+)-norpatchoulenol has appeared in the literature. The first such synthesis from commercially available, optically active, (+)-10-camphorsulfonic acid is described in the first chapter of this thesis.

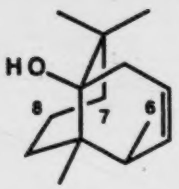
Results and Discussion

Several synthetic schemes can be envisioned to provide our target compound, norpatchoulenol (**15**). I shall briefly discuss a number of these approaches.

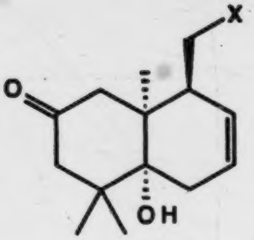


15

Let us consider, for example, the cleavage of the C-6, C-7 bond, process **a**. It involves the preparation of a molecule of the type of **66**.



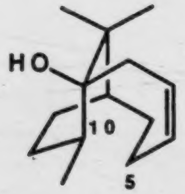
66



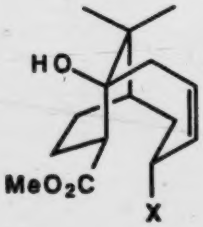
67

This molecule should be functionalized in a manner that permits subsequent cyclization, for example, by means of a carbonyl group at C-8 to activate position C-7 towards the abstraction of a proton, and also a leaving group at C-6. This would lead to derivative **67**.

A less accessible model results schematically from the cleavage of the C-5, C-10 bond (process **b**). This requires the preliminary synthesis of molecule **68**, which is *a priori* difficult to obtain. In addition, suitable activation of C-5 and C-10 is necessary. This could be visualized as in compound **69**, with a carbomethoxy group at C-10 and an allylic leaving group. All these, without taking into account many stereochemical problems, makes it a difficult target.

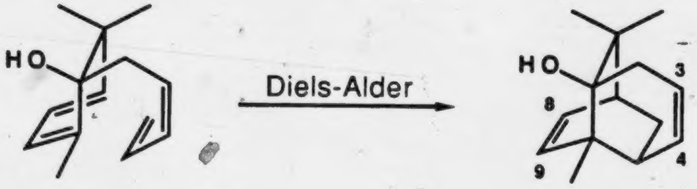


68



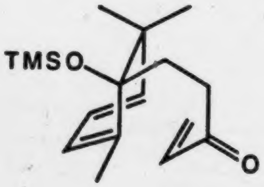
69

Another approach originates from the simultaneous cleavage of both the C-5, C-10 and C-6, C-7 bonds, which requires precursor **70**. This approach has been used by Frater[40] and Yoshikoshi[41] *et al.* for the synthesis of seychellene (**8**), and by Näf and coworkers[26,27] for the preparation of patchouli alcohol. In the present case, the preexistence of the 3,4 double bond would pose a serious problem concerning the selective hydrogenation of the C-8, C-9-double bond.



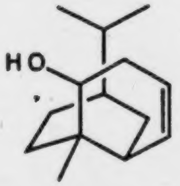
70

A precursor of the C-3, C-4-double bond is therefore required, such as a carbonyl group at C-4. Compound **71** possesses this feature and has been used by Oppolzer and Snowden[37] in their synthesis of racemic norpatchoulenol.

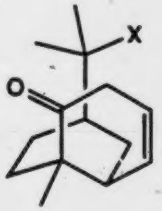


71

Disconnection of carbons 1 and 11 (process **c**) leads to a molecule with the skeleton of **72**, functionalized as in **73**. The intramolecular cyclization of ε-haloketones is a known process[42-44] and could be used to effect the ring closure.

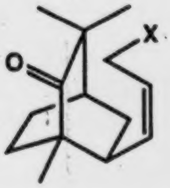


72



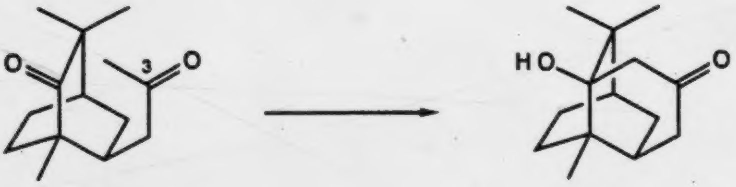
73

This reaction can also be utilized if the cleavage of the C-1, C-2 bond (process **d**) is considered. Such a procedure would require the preparation of a compound like **74**. The syntheses of patchouli alcohol reported by Danishefsky,[24] Mirrington[25] and Teisseire[29,30] are based on this methodology, as are those of norpatchoulenol published by Teisseire.[30,36,38]



74

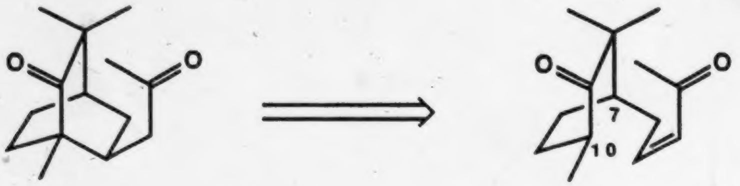
Another type of reaction using process **d** involves a possible internal aldol condensation of diketone **75** to form hydroxy-ketone **76**. The carbonyl group at C-3 could then be manipulated to produce the desired double bond by a reduction-dehydration sequence or by means of a Bamford-Stevens reaction.



75 **76**

We set our goal to the preparation of the naturally occurring, optically active, (+)-norpatchoulenol (**15**). An analysis of the approaches mentioned above suggests that process **d**, the retrosynthetic disconnection of the C-1, C-2-bond, is the course of action that permits the best degree of control over the absolute stereochemistry of the final product and the related intermediates. We decided to address the problem of forming the third ring in the patchoulane system by means of the intramolecular aldolization of compound **75**, since this method looked very promising and had never been reported before.

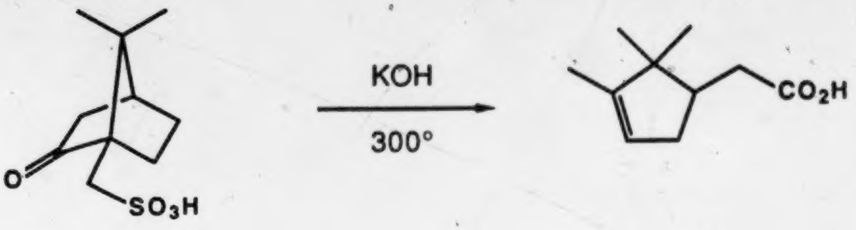
From the retrosynthetic analysis, the immediate task at hand was to prepare the bicyclo[2.2.2]octane derivative **75** with high stereoselectivity. The diketone could be envisaged to originate from an intramolecular Michael addition of the C-10 enolate in **77** onto the side-chain unsaturated ketone:



75 **77**

Note that the absolute stereochemistry of the desired final product will be controlled solely by that of C-7 alone. The shown 7R configuration would lead to (+)-norpatchoulenol, whereas the 7S epimer would produce the unnatural (-)-isomer The absolute stereochemistry at C-10, the only other chiral center in **77**, is unimportant since the reaction requires the formation of the corresponding enolate, which would destroy the chirality at this position. This brings up a point in favor of the approach that we decided to follow: if the stereochemistry at the C-7 center can be controlled in a stereoselective and stereospecific manner, both the natural and the unnatural antipodes of norpatchoulenol can be prepared using the same method.

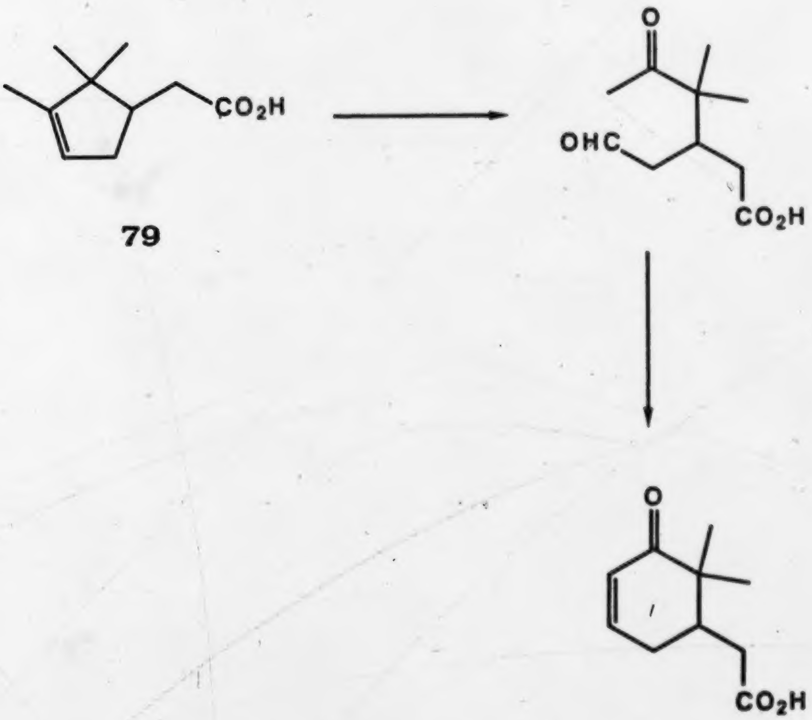
Campholenic acid (**79**) can be prepared by alkali fusion of camphorsulfonic acid (**78**).[45]


KOH
300°
O
SO$_3$H
CO$_2$H

78 **79**

Cleavage of the double bond in **79** by ozonolysis followed by recyclization would produce the unsaturated keto-acid **80** (Scheme 14).

Scheme 14

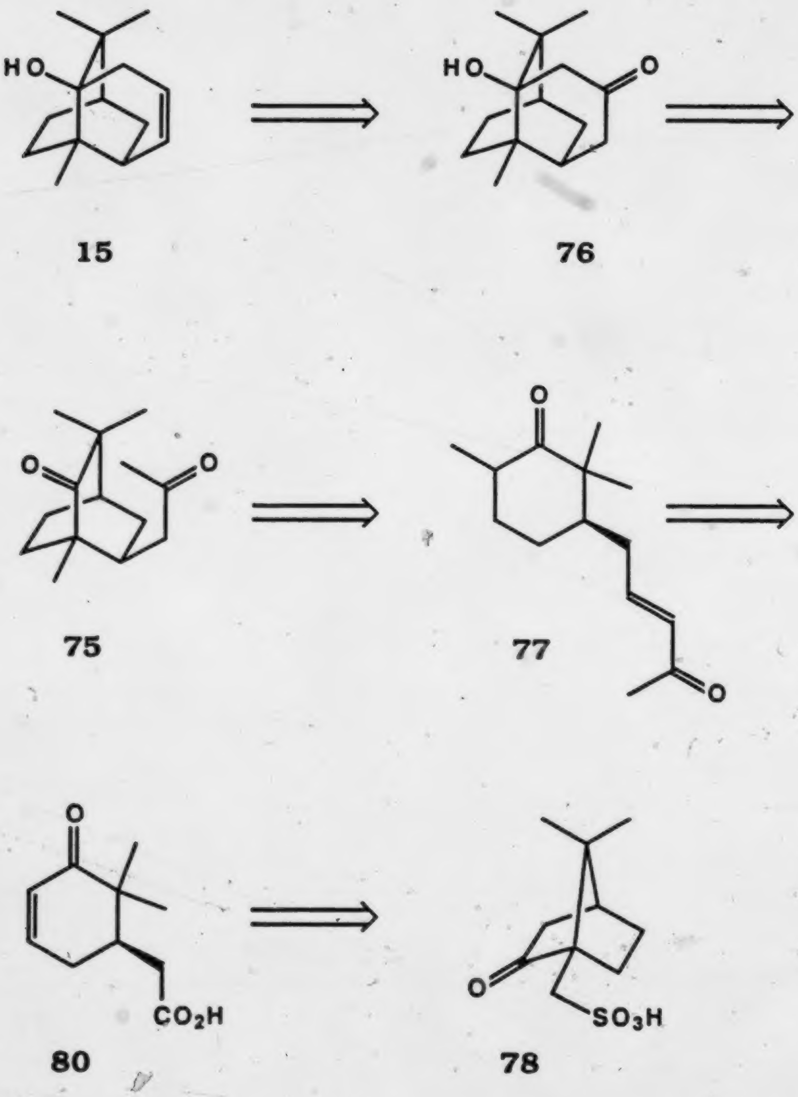

CO$_2$H
79
O
OHC
CO$_2$H
O
CO$_2$H

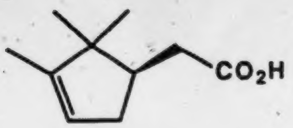
80

Since the only chiral center in campholenic acid does not participate in any of the reactions in the sequence, and since both enantiomers of camphorsulfonic acid are commercially available in very high optical purity, the stereochemistry of the intermediates in our synthesis, and therefore that of the final product, can be easily controlled. Compound **80** can then be converted into **77** by the introduction of a methyl group at C-10, followed by extension of the side chain by three carbon atoms and the necessary functional group manipulations. The full retrosynthetic pathway is shown in Scheme 15.

In the present context, (1S)-(+)-camphorsulfonic acid (**78**) was reacted with fused potassium hydroxide at *ca.* 400°C to provide (+)-campholenic acid (**81**)[45] in 80% yield. Compound **81** displayed a specific rotation $[\alpha]_D^{22}$ +9.2° (c = 0.98, $CHCl_3$), in close agreement with the reported[46] value. It also showed a molecular ion peak at m/z 168.1148 in the mass spectrum, consistent with the molecular formula $C_{10}H_{16}O_2$. Its infrared spectrum showed the presence of a carboxylic acid at 3500-2300 and 1705 cm^{-1} . The ^1H nmr spectrum exhibited methyl groups at δ 0.82, 1.03 and 1.61, as well as a vinylic proton at δ 5.24. The structure was also confirmed by the ^{13}C nmr APT spectrum, which shows signals for methyl groups at δ 12.26, 19.60 and 25.40, olefinic carbon atoms at δ 121.55 and 147.55, and the carbonyl group at δ 180.21.

Scheme 15


HO
HO
O
15
76
O
O
O
75
77
O
O
CO₂H
SO₃H
80
78



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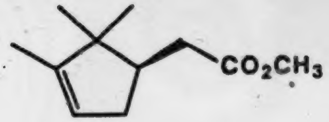
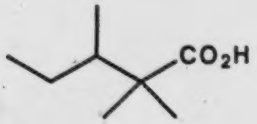


82

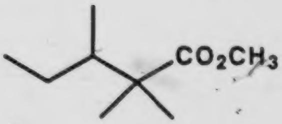
The transformation of the acid **81** into the methyl ester **82** was effected in 98% yield upon treatment with potassium carbonate suspended in acetone, followed by the addition of an excess of methyl iodide at room temperature. Compound **82** showed a specific rotation $[\alpha]_D^{22}$ +12.0° and an ester carbonyl at 1740 cm^{-1} in the infrared spectrum. Its mass spectrum presented a molecular ion peak at m/z 182.1297 and in the ^1H nmr spectrum the methoxy group was observed as a singlet at δ 3.67. The carbonyl group also appeared as a singlet at δ 174.09 in the ^{13}C nmr spectrum.

The preliminary studies for the present work were carried out using racemic materials. Racemic **81** and **82** were prepared in an analogous manner from (±)-camphorsulfonic acid sodium salt. Interestingly, when the fusion reaction was carried out using the sodium salt, a second product was obtained together with campholenic acid. The two compounds could be partially separated by fractional vacuum distillation. The byproduct so obtained displayed bands for a carboxylic acid at 3500-2400 and 1700 cm^{-1} in the infrared spectrum, and a peak at m/z 115.0757 in the mass spectrum. The ^1H nmr spectrum showed complex signals at δ 1.68, 1.46 and 0.99 with an integral of one proton each, methyl singlets at δ 1.12 and 1.11, a methyl triplet at δ 0.92 and a methyl doublet at δ 0.77. Its ^{13}C nmr APT (Attached Proton Test) spectrum displayed a carbonyl peak at δ 185.92 and seven other signals: four quartets, one doublet, one triplet and one singlet.

The presence of the two methyl singlets, coupled with the appearance of a carbon singlet (other than the carbonyl group) suggests the presence of a *gem*-dimethyl group in the compound. Also, the methyl triplet and doublet in the proton spectrum are indicative of an ethyl and a CH_3-CHR- groups respectively. This spectral data is in accordance with the structure **83** for the secondary product. The electron impact mass spectrum of **83** did not show a molecular ion peak, but the chemical ionization mass spectrum displayed a base peak at m/z 162 ($[M + 18]^+$), corresponding to the expected molecular formula for the ammonia cluster of the acid ($C_8H_{19}O_2N$).



83

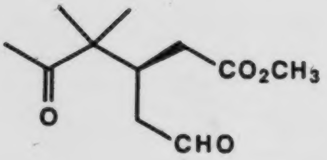


84

Complete separation of the byproduct from campholenic acid was achieved after the formation of the corresponding methyl ester, using the same procedure as above. The products were separated by fractional distillation and the isolation of compound **84** confirmed the presence of a carboxylic acid in the structure of the secondary product. Compound **84** displayed a molecular ion peak at m/z 158.1305 in the mass spectrum, in accordance with the molecular formula $C_9H_{18}O_2$. Its ^1H nmr spectrum shows a signal at δ 3.65 for the methoxy group and a set of signals equivalent to those of the corresponding free acid. A band at 1735 cm^{-1} in the infrared spectrum also confirms the presence of an ester moiety.

The mechanism by means of which compound **83** is formed is not known. The fact that the product was only obtained from the sodium salt of camphorsulfonic acid indicates that more severe conditions are required for its formation, since higher temperatures were used for the fusion of this salt. When the reaction was carried out at lower temperatures, only campholenic acid was obtained. This suggests that the byproduct could be formed from the campholenic acid salt, and not directly from the camphorsulfonic acid. Further investigations are in progress to settle this point.

Compound **82** was subjected to ozonolysis at -78°C in a mixture of methanol and dichloromethane. Reductive workup using triphenylphosphine[48]* gave ketoaldehyde **85**. Attempts to purify this substance failed, resulting in substantial decomposition and loss of material. This compound was, therefore, immediately treated with p-toluenesulfonic acid in refluxing benzene, to afford enone-ester **86**, $[\alpha]_D^{22}$ +58.0°, in 80% yield from **82**. The infrared spectrum presented carbonyl bands at 1730 and 1680 cm^{-1} and its mass spectrum showed a molecular ion peak at m/z 196.1098, consistent with the formula $C_{11}H_{16}O_3$. The ^1H nmr spectrum displayed two doublets of doublets at δ 6.83 and 5.97 for the vinylic protons and sharp singlets at δ 3.70 for the methoxy group and at δ 1.18 and 1.01 for the other two methyl groups. The presence of the double bond was confirmed by doublets at δ 143.13 and 127.69 in the ^{13}C nmr APT spectrum, which also showed carbonyl signals at δ 202.42 and 172.38.



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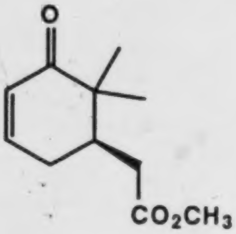

86

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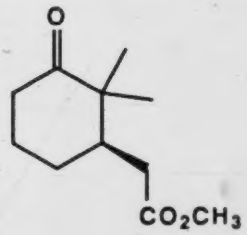
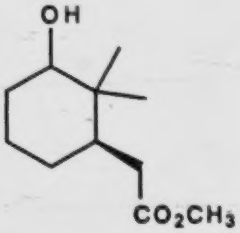
* Work carried out in our laboratories[47] has shown that the use of dimethyl sulfide is ineffective and a single ozonide is isolated.

Hydrogenation of the unsaturated keto-ester **86** at 10-20 psig in ethyl acetate solution using Adams catalyst (PtO_2) gave a 9:1 mixture of keto-ester **87** and hydroxy-ester **88** in a total yield of 96%. Compound **87** showed carbonyl bands at 1740 (ester) and 1710 cm^{-1} (ketone). Its ^1H nmr and ^{13}C nmr spectra did not display any signals in the vinylic or double bond regions. A molecular ion peak at m/z 198.1255 confirmed the molecular formula $C_{11}H_{18}O_3$.



87

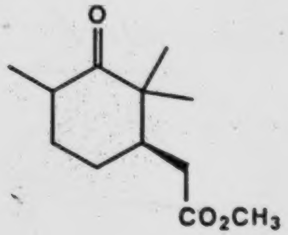


88

The alcohol **88**, on the other hand, presented a broad band at 3200-3600 cm^{-1} in the infrared spectrum and a molecular ion peak at m/z 200.1416, in accordance with the structure depicted.

The formation of the hydroxy-ester during the hydrogenation reaction was avoided by using a different catalyst. Thus, treatment of a solution of compound **86** in ethyl acetate with hydrogen at 10-20 psig in the presence of 5% palladium over carbon afforded a 97% yield of keto-ester **87**.

The monomethylation of **87** was thought, at first, to be an easily achievable task. Deprotonation of the substance with a suitable base followed by addition of methyl iodide should give compound **89**. The generation of the dimethylation product, **90**, was not expected to represent a problem, since the introduction of the second methyl group onto an already sterically crowded position was not very likely. Therefore, we proceeded to carry out the alkylation by treatment of the dimethyl keto-ester **87** with two equivalents of sodium hydride in 1,2-dimethoxyethane solution. After stirring at room temperature for three hours, 1.2 equivalents of methyl iodide were added and the mixture was allowed to react at room temperature. After the workup, a 2:1:3 mixture of starting material (**87**), **89** and **90** was obtained in 66% yield.



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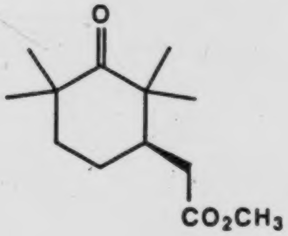
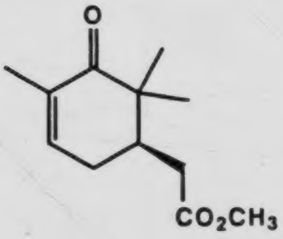


90

To reduce the amount of dimethylation product, we decided to decrease the amount of base used. When the reaction was effected with 1.1 equivalents of sodium hydride, an 83% yield of a 1:5:2 mixture of the same compounds was produced. Lowering the reaction temperature and increasing the reaction time reduced the amount of starting material recovered, but only at the cost of increasing the extent of dimethylation. These results were still unacceptable, especially due to the fact that the separation of **89** from **90** proved to be extremely difficult, requiring an objectionable number of recycling steps in the chromatographic process. The goal at hand then, was the elimination of the tetramethyl keto-ester **90** as a product of the reaction.

An alternate route was considered at this point: the alkylation process could be carried out before the hydrogenation step. Treatment of enone-ester **86** with sodium hydride at room temperature, followed by the addition of methyl iodide, gave a 1:2 mixture of compounds **91** and **92** in only 23% yield. The ^{1}H nmr spectrum of the conjugated enone-ester **91** displayed a characteristic low field signal at δ 6.58 for the vinyl proton, and a molecular ion peak at m/z 210.1251 in its mass spectrum. Compound **92**, on the other hand, showed a peak at higher field (δ 5.68) which integrated for two protons.



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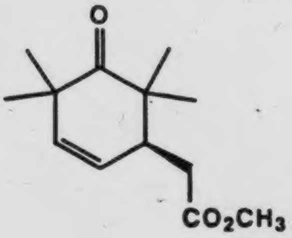
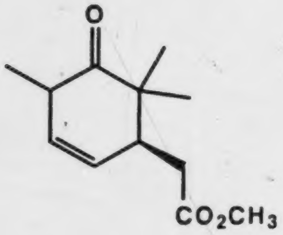


92

This outcome was not totally unexpected. Dialkylation is known to be a major problem during the alkylation of α,β-unsaturated ketone,[49-52] because a proton is abstracted more easily from the intermediate β,γ-unsaturated ketone (**93**) than from the starting material (**86**).[53]



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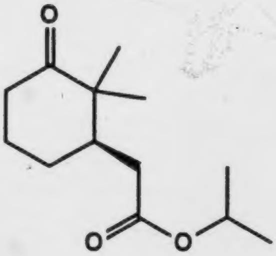
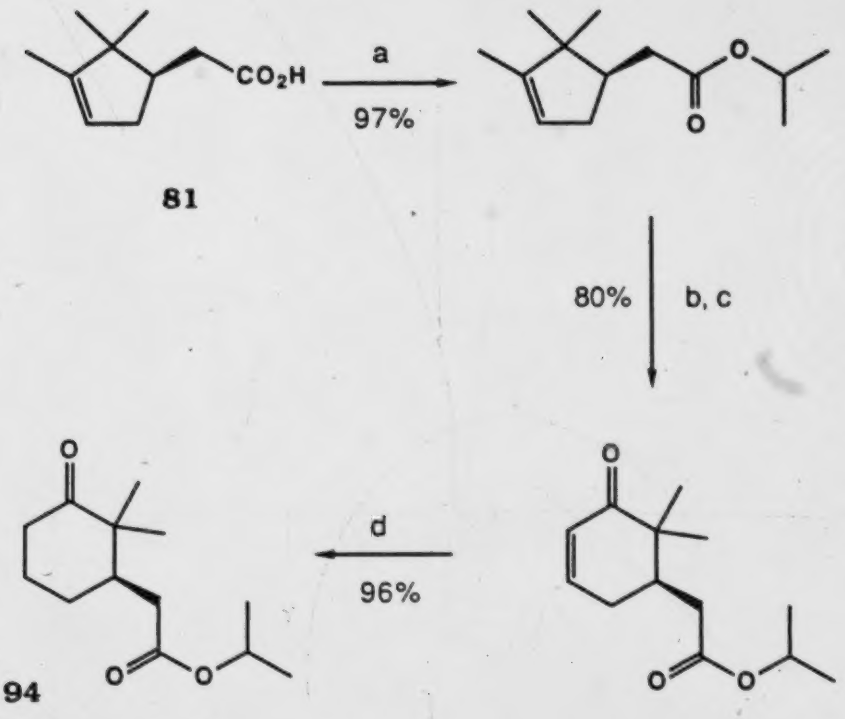


94

In the hope that increasing the steric bulk at the ester position could have some effect upon the alkylation reaction, we decided to prepare an ester of higher molecular weight. The isopropyl ester **94** was prepared in a manner analogous to the sequence already described for the methyl ester **87** (Scheme 16). Treatment of **94** with sodium hydride in dimethoxyethane followed by addition of methyl iodide at room temperature gave a 1:4:2 mixture of starting material and the corresponding monomethylated and dimethylated products.

Scheme 16.



(a) 1) K_2CO_3, acetone; 2) $(CH_3)_2CHI$, reflux, 20 h; (b) 1) O_3, CH_2Cl_2, CH_3OH, -78°C; 2) $(C_6H_5)_3P$, -78° → 25°C; (c) TsOH, benzene, reflux, $-H_2O$; (d) H_2, EtOAc, 5% Pd/C.

Since none of the procedures attempted up to this point showed a significant improvement of the reaction, we resolved to try other bases for the deprotonation step. Lithium diisopropylamide, potassium hydride and potassium hexamethyldisilazide[54] were tested under various conditions. The results are summarized in Table 1.

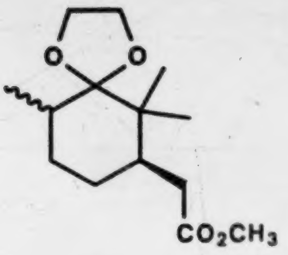
Table 1. Reaction conditions and product yields for the methylation of compound **87**.

Entry	Base	No. Eq.	No. Eq. CH_3I	Temp. (°C)	Time (hr.)	Yield(%) Mono	Di	S.M.
1	NaH	2.0	1.2	25	42	12	34	20
2	NaH	1.1	1.2	25	22	53	18	12
3	NaH	1.2	1.1	0	36	55	26	<5
4	LDA	1.7	2.0	-35	6	49	16	15
5	KH	1.1	1.2	25	6	31	13	26
6	KH	1.2	1.2	0	5	35	17	20
7	KH	1.1	2.0	-30	7	58	7	14
8	KH	1.3	2.0	-50	14	65	10	7
9	KHMDS	1.2	6.0	-78	2	77	0	0

The best conditions achieved (entry 9) involved the treatment of keto-ester **87** with potassium hexamethyldisilazide at -78°C, followed by the addition of a large excess of methyl iodide, also at low temperature, to give a 77% yield of pure monomethylated product, **89**. Unfortunately, scaling up the reaction over 500 milligrams brought about the unavoidable formation of the dialkylated material, **90**, in amounts varying from 5 to 20% of the isolated product. It should be noted that the monoalkylated compound was always obtained as a mixture of epimers at the alpha position in ratios varying from 1:1 to 5:1, depending on the reaction conditions. Its ^1H nmr spectrum clearly showed two sets of signals for the methoxy group, the alpha proton and the methyl groups. The mass spectrum displayed the molecular ion at m/z 212.1416. The dialkylated compound, **90**, presented four methyl singlets in the ^1H nmr spectrum, and a molecular ion peak at m/z 226.1570 in the mass spectrum. The infrared spectrum of both substances showed carbonyl bands at 1730 and 1700 cm^{-1} .

With the keto-ester **89** in hand, we had then to increase the length of the side chain by three carbon atoms to form the α,β-unsaturated diketone **77** and then to carry out a cyclization *via* Michael addition. The simplest way to effect the above transformations would be to replace the ester group with an aldehyde and then extend the chain with a suitable Wittig-type reagent.

To this effect, the ketone was protected as a ketal by treatment of **89** with p-toluenesulfonic acid and an excess of ethylene glycol in benzene at reflux temperature, to produce compound **95** in quantitative yield. The ^1H nmr spectrum of **95** showed a complex signal centered at δ 3.98 with an integral of four, representing the protons on the ketal portion of the molecule. Its infrared spectrum had only one band corresponding to an ester carbonyl at 1740 cm^{-1}. A molecular ion peak at m/z 256.1680 in the high resolution mass spectrum was in accordance with the molecular formula $C_{14}H_{24}O_4$.



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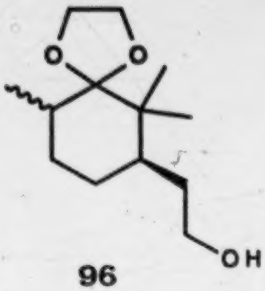
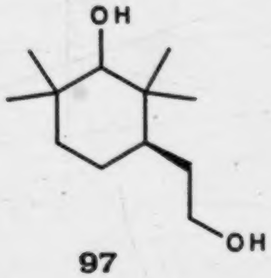


96

Reduction of the ester moiety to give the hydroxy-ketals **96** was carried out in 94% yield with lithium aluminum hydride in refluxing ethyl ether, followed by alkaline workup. The ^1H nmr spectrum displayed the protons at the base of the hydroxyl group as a multiplet at δ 3.62. The infrared spectrum showed a broad band at 3700-3100 cm^{-1} , characteristic of an alcohol, and no signals in the carbonyl region. A molecular ion peak at m/z 228.1726 confirmed the formula $C_{13}H_{24}O_3$.

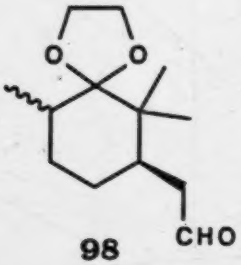
An alternate and more convenient method for the separation of compounds **89** and **90** was realized chemically. The crude mixture from the methylation reaction was subjected to ketalization, producing the ketal-ester **95**. The tetramethyl keto-ester **90** did not form the corresponding ketal, presumably due to the steric hinderance exerted by the four methyl groups onto the ketone carbonyl. Unfortunately, chromatographic separation of these two compounds proved to be just as difficult. Lithium aluminum hydride reduction of the mixture of substances gave hydroxy-ketal **96** and diol **97**. The bulk of compound **97** could be separated by precipitation upon cooling of a hexane solution of the crude reaction products. Further purification of **96** was achieved by either flash chromatography or High Performance Medium Pressure Liquid Chromatography (HPMPLC). The infrared spectrum of **97** showed a band at 3500-3000 cm^{-1}. Its mass spectrum did not display a molecular ion peak, but a M-18 peak was present at m/z 182.1678



97

due to the facile loss of a molecule of water. The ^1H nmr spectrum had two complex signals at δ 3.74 and 3.61, corresponding to the two protons adjacent to the hydroxyl group on the side chain, a doublet at δ 2.93 for the proton at the base of the secondary alcohol, and methyl groups at δ 1.02, 0.97, 0.89 and 0.78. The ^{13}C nmr spectrum clearly presented the carbon atoms bearing oxygen at δ 84.49 and 61.95.

The oxidation of compound **96** to the corresponding aldehyde turned out to be a more laborious task. Treatment of **96** with pyridinium dichromate[55] in dichloromethane solution afforded a mixture that showed at least five spots in thin layer chromatography. A similar result was obtained with pyridinium chlorochromate.[56] Cheng and coworkers have reported the use of pyridinium chlorochromate adsorbed on alumina for the mild oxidation of sensitive alcohols.[57] When the hydroxy-ketal was exposed to this reagent in hexane solution, a cleaner reaction resulted, and the ketal-aldehydes **98** were isolated in 68% yield. An improved yield of 79% was realized when the oxidation was carried out with pyridinium chlorochromate in dichloromethane solution, in the presence of sodium acetate as a buffer.[55] The mixture of epimers **98** showed a complex signal at δ 9.72 and two sets of methyl groups in the 200 MHz ^{1}H nmr spectrum. The infrared spectrum had bands at 2890 and 1725 cm^{-1} , which correspond to the aldehyde function, and the mass spectrum displayed a molecular ion peak at m/z 226.1569, in full accordance with the molecular formula $C_{13}H_{22}O_3$.



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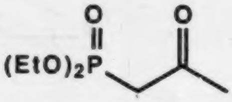
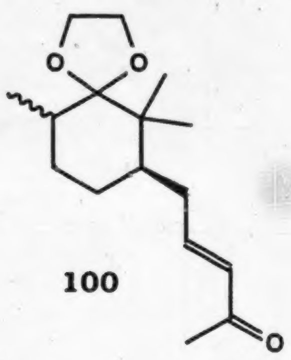


99

Compound **98** had the functional groups required for the subsequent steps, and we could then proceed to extend the side-chain and cyclize. Diethyl 2-oxopropylphosphonate (**99**) was reacted with sodium methoxide in methanol to form the corresponding sodium salt, and then a solution of **98** in methanol was added. Stirring the mixture at room temperature for 18 hours, followed by workup, gave the crude material **100**, which was used without purification for the next reaction. Refluxing compound **100** in a 1:1 mixture of 3N hydrochloric acid and tetrahydrofuran for four hours brought about the hydrolysis of the acetal group, with concomitant cyclization via Michael addition . Two major products were discernible on TLC, and separation was achieved by flash chromatography or HPMPLC. Each of these compounds showed a broad band centered at 1705 cm^{-1} in the infrared spectrum. Molecular ion peaks were observed at m/z 222.1620 and 222.1622 in the high resolution mass spectra, which are consistent with the molecular formula $C_{14}H_{22}O_2$. These spectral data suggest structures **101** and **102**. Individual assignment of these structures was made with the basis of high resolution (400 MHz ^1H and 100 MHz ^{13}C) nmr spectroscopy. The spectral data are shown in Tables 2 to 5.



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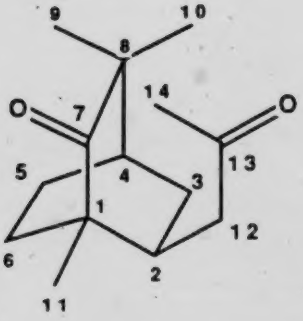
Homonuclear and heteronuclear correlation spectra were also acquired and are shown in Figures 1 to 4.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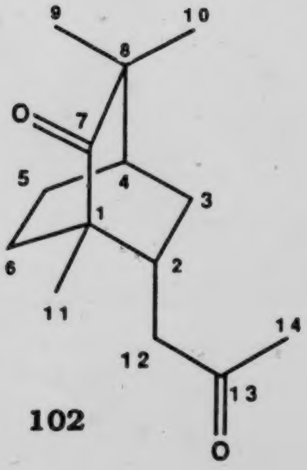
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102

Table 2. 400 MHz ^{1}H nmr data for compound **101**.

Proton	Chemical Shift (δ)	Multiplicity (coupling constants/Hz)
H-12a or H-12b	2.54	dd (4.0, 17)
H-2	2.34	dddd (4.0, 6.0, 10, 11)
H-14	2.12	s
H5-α or H5-β	2.04	ddd (3.0, 11, 14)
H-12b or H-12a	2.00	dd (11, 17)
	1.97	complex
	1.69 (4H)	complex
H3-α or H3-β	1.37	doublet of quintets (3.0, 14)
H-9 or H-10	1.13	s
H-10 or H-9	1.08	s
H-11	0.86	s

Table 3. 100 MHz ^{13}C nmr data for compound **101**.

Carbon	Chemical Shift (δ)	Multiplicity
C-13 or C-7	220.6	s
C-7 or C-13	206.6	s
C-12	48.0	t
C-1 or C-8	45.3	s
C-8 or C-1	45.2	s
C-4	38.3	d
C-2	36.8	d
C-6	31.2	t
C-3	31.1	t
C-14	30.1	q
C-9 or C-10	24.6	q
C-10 or C-9	22.7	q
C-5	22.0	t
C-11	17.9	q

Table 4. 400 MHz ^{1}H nmr data for compound **102**.

Proton	Chemical Shift (δ)	Multiplicity (coupling constant in Hz)
H-12a or H-12b	2.60	dd (4.0, 16)
H-12b or H-12a	2.48	dd (11, 16)
H3-β	2.34	dddd (3.0, 3.5, 11, 14)
H-14	2.17	s
H-2	2.14	complex
H5-β	1.92	ddd (3.5, 7.0, 11, 13)
H-6α	1.78	ddd (4.0, 11.5, 14)
H-4	1.66	apparent quintet (3.0)
H5-α	1.54	dddd (3.0, 5.0, 11, 13)
H6-β	1.44	dddd (2.0, 5.5, 12, 14)
H-10	1.16	s
H-9	1.12	s
H-3α	1.06	ddd (2.5, 6.0, 14)
H-11	0.88	s

Table 5. 100 MHz ^{13}C nmr data for compound **102**.

Carbon	Chemical Shift (δ)	Multiplicity
C-13 or C-7	221.0	s
C-7 or C-13	207.3	s
C-12	45.8	t
C-1 or C-8	44.8	s
C-8 or C-1	44.5	s
C-4	37.9	d
C-2	32.4	d
C-3	31.6	t
C-14	30.2	q
C-6	25.2	t
C-9	24.2	q
C-10	24.1	q
C-5	22.7	t
C-11	17.9	q

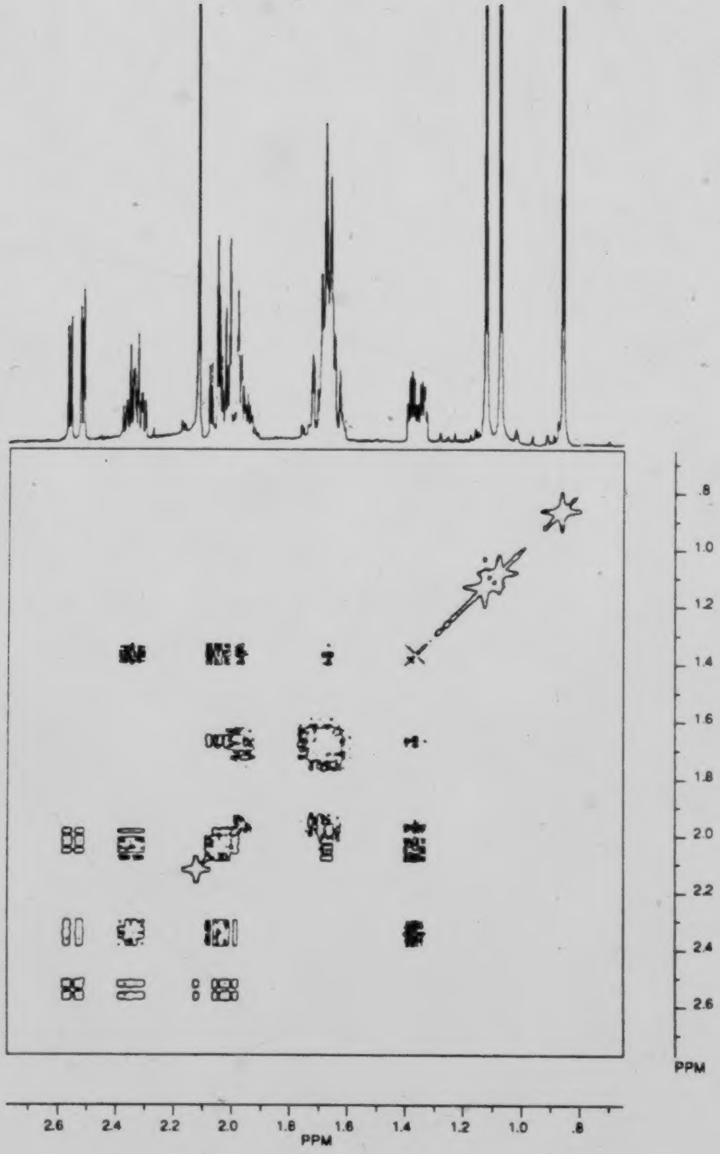


Figure 1. COSY-90 Spectrum of **101**.

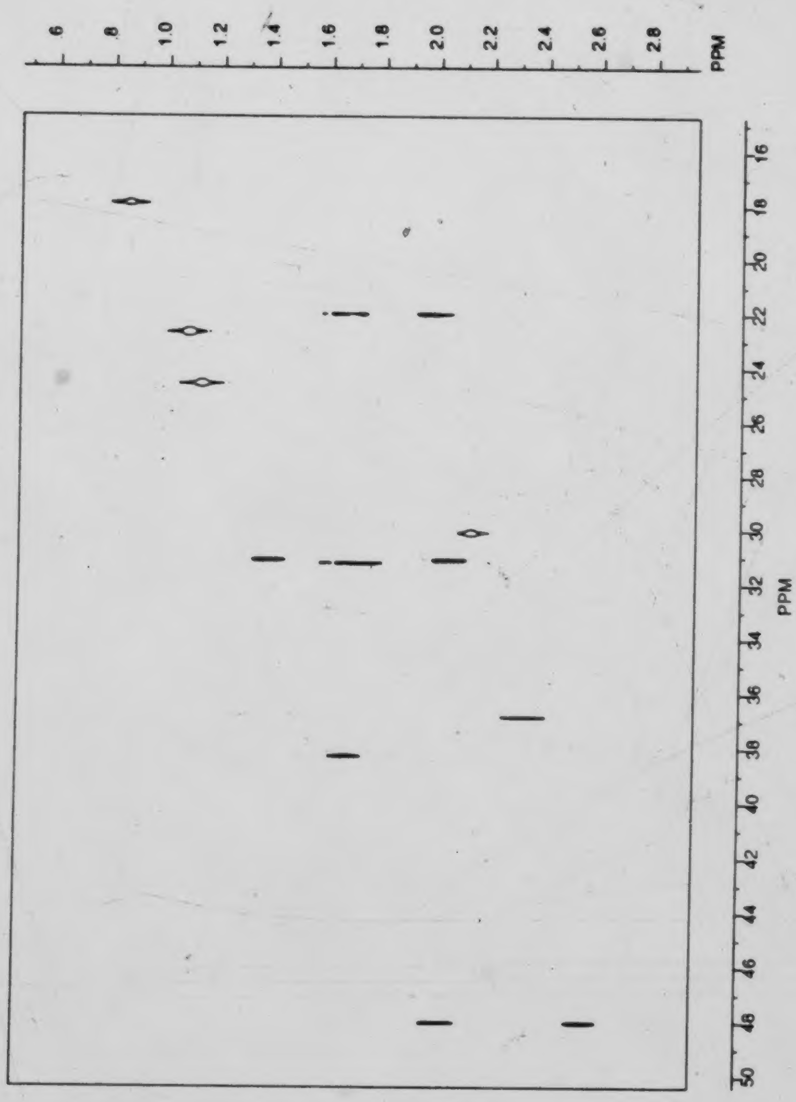


Figure 2. ^{1}H-^{13}C Correlation Spectrum of **101**.

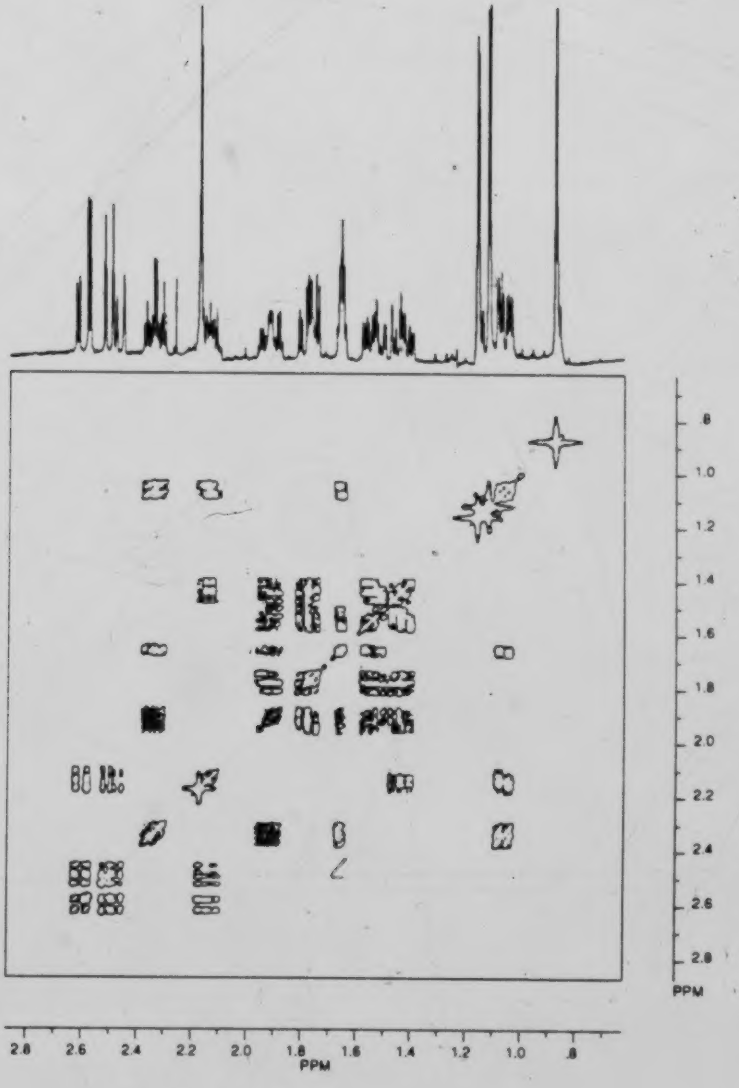


Figure 3. COSY-90 Spectrum of **102**.

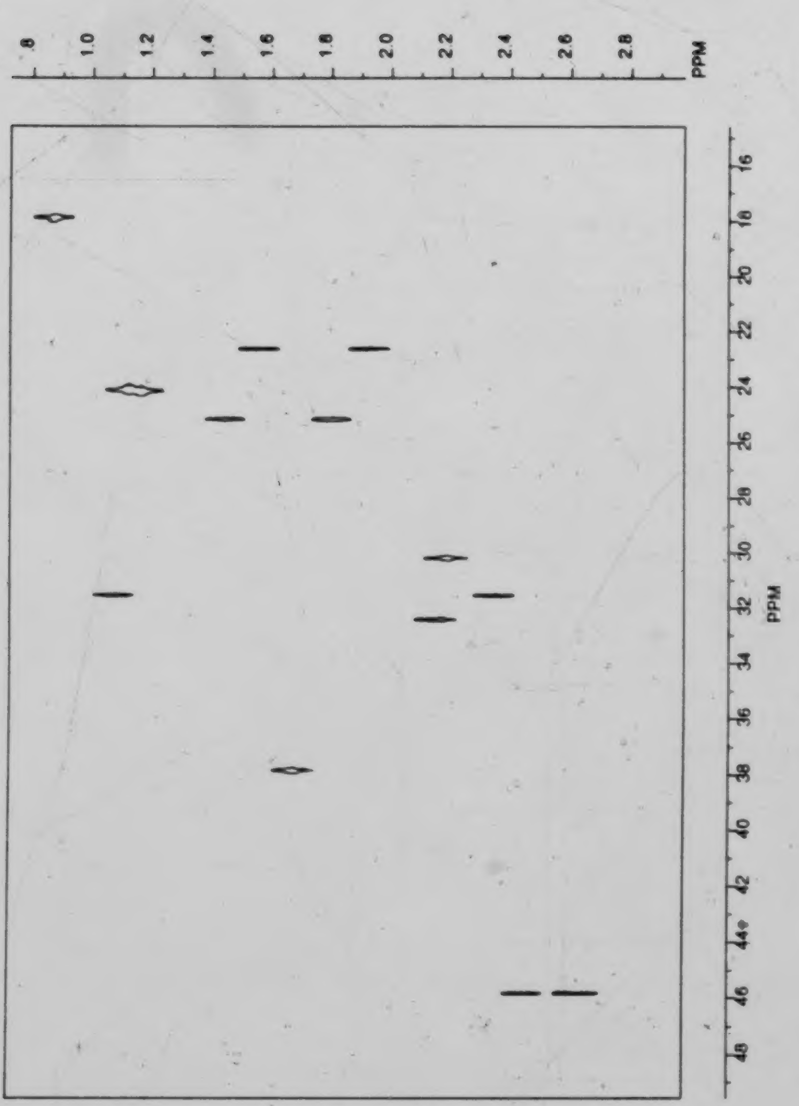
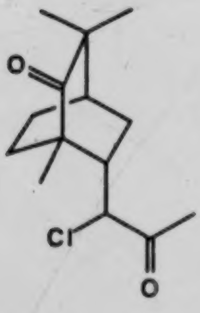


Figure 4. ^{1}H-^{13}C Correlation Spectrum of **102**.

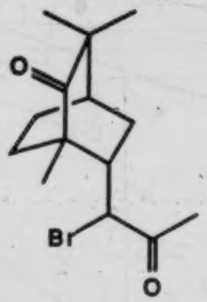
For the diketone **102** the assignment followed the rationale described below. The two doublets of doublets at low field in the ^{1}H nmr were ascribed to the protons attached to C-12. This was confirmed by the appearance of C-12 as a triplet at δ 48.0 in the ^{13}C nmr spectrum. The ^{1}H COSY spectrum showed that these two signals were coupled to one another and to the peak at δ 2.14, which is therefore assigned to H-2. In turn, H-2 showed couplings to H-3β and to H-3α at δ 2.34 and 1.06, respectively. Both of these peaks are correlated to the carbon atom appearing at δ 31.4. Also, a coupling of H-2 with the signal at δ 1.44 allowed the assignment of the latter to H-6β (W coupling). From the ^{1}H-^{13}C correlation spectrum, H-6α is allotted the peak at δ 1.78. The quintet at δ 1.66 was assigned to H-4 on the basis of its multiplicity. This was endorsed by the fact that the corresponding carbon atom is the only other doublet in the ^{13}C nmr spectrum. Other than the methyl groups, the only two signals left unassigned at this point, at δ 1.92 and 1.54, were attributed to H-5β and H-5α, respectively. The methyl groups were assigned on the basis of NOE experiments. Saturation of H-9 (δ 1.12) gave rise to a 2% enhancement on each of H-4 (δ 1.66), H-5β (δ 1.92) and H-6β (δ 1.44). Similarly, irradiation of H-10 resulted in NOE enhancements of 4% for H-3β (δ 2.34) and 2% for H-4 (δ 1.66). Finally, saturation of H-11 originated an NOE of 6% on H-14 (δ 2.17) and of -7% on H-10 (δ 1.16). The signals in the nmr spectra for compound **101** were assigned in a similar manner. Unfortunately, the higher degree of overlapping in its ^{1}H nmr spectrum precluded the unequivocal assignment of every peak.

Ultimate proof of the relative stereochemistry of **101** and **102** at C-2 was achieved by means of the chemical transformations described below.

Since diketone **102** represented 50% of the product mixture obtained from the reaction, it was desirable to convert it into the required epimer **101**. Presumably this could be done by means of a halogenation - dehydrohalogenation - hydrogenation sequence. Toward this end, we attempted to prepare the α-chloroketone **103** by treatment of **102** with sulfuryl chloride in carbon tetrachloride solution. However, only starting material was recovered after the workup of the reaction mixture. Bromination, on the other hand, turned out to be more successful. When compound **102** was reacted with pyridinium bromide perbromide[59,60] and acetic acid in dichloromethane solution at room temperature, a 2:1 mixture of monobrominated diketone **104** and dibrominated compound **105** was obtained in 67% yield.



103



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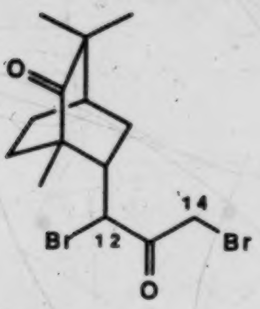
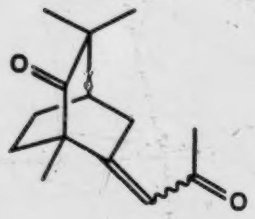


105

Compound **104** displayed a doublet at δ 4.63, corresponding to the proton adjacent to the bromine atom, and the methyl ketone at δ 2.38 in the ^{1}H nmr spectrum. Its mass spectrum showed two molecular ion peaks at m/z 302.0702 and 300.0724, in accordance with the molecular formula $C_{14}H_{21}O_2Br$. The dibromide **105**, on the other hand, showed H-12 as a doublet at δ 5.09 and also doublets at δ 4.39 and 4.06, representing the two protons on C-14. The mass spectrum showed three peaks at m/z 381.9785, 379.9808 and 377.9830 in a 1:2:1 intensity ratio, as expected for the formula $C_{14}H_{20}O_2Br_2$. Lowering the temperature of the reaction to 0°C increased the total yield to 81% and the ratio of **104** to **105** to 4:1. At -10°C the monobrominated compound was obtained exclusively in essentially quantitative yield.

An attempt to dehydrobrominate **104** by refluxing in pyridine[61] only produced what by TLC appeared to be a complex mixture of substances. However, when the base was changed to 1,4-diazabicyclo[2.2.2]octane (DABCO)[62,63] and the reaction was carried out in dichloromethane at room temperature, the α,β-unsaturated diketone **106** was obtained in 76% yield. The ^{1}H nmr spectrum of

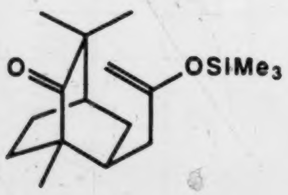


106

this compound showed a vinyl proton signal at δ 6.12. The stereochemistry around the carbon-carbon double bond is not known and, in view of the next reaction, is irrelevant to the purpose of our scheme. Completion of the sequence was achieved by hydrogenation of **106** at atmospheric pressure using PtO_2 as a catalyst, to afford the desired isomer **101** in quantitative yield.

With compound **101** in hand, we were set up to attempt the intramolecular cyclization that would form the third ring and complete the patchoulane skeleton. For this purpose the generation of a carbanion at the C-14 position, which would then add to the C-7 carbonyl group, seemed to be the reasonable route to follow. Unfortunately, our efforts to effect the above transformation under various conditions proved fruitless. Treatment of **101** with sodium methoxide in methanol or lithium diisopropylamide in tetrahydrofuran or dimethoxyethane at low temperature always resulted in the recovery of the unchanged starting material.

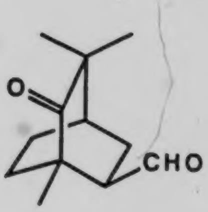
Mukaiyama and coworkers[64] have reported the reaction of silyl enol ethers with aldehydes and ketones, in the presence of titanium tetrachloride under mild conditions, to give cross-aldol addition products in good yield. To apply this methodology to our case, it became necessary to prepare the silyl enol ether **107**. This was done in 72% yield by treatment of **101** with lithium diisopropylamide in tetrahydrofuran at -78°C, followed by addition of an excess of a 1:1 mixture of triethylamine and trimethylsilyl chloride. Compound **107** displayed broad singlets at δ 4.06 and 3.98, corroborating the presence of the two vinyl protons. Moreover, a large singlet at δ 0.21 confirmed the presence of the trimethylsilyl group in the molecule.



107

Having obtained the desired enol ether, we moved along to attempt Mukaiyama's reaction. Not totally unexpectedly, in view of our previous results, treatment of **107** with a 0.1 M solution of titanium tetrachloride in dichloromethane at -78°C resulted only in the hydrolysis of the silyl enol ether during the workup, to give diketone **101**.

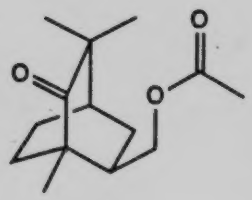
Due to the failure of our cyclization attempts to this point, we decided to try a different approach to generate the third ring of norpatchoulenol. Baeyer-Villiger oxidation of **101** followed by hydrolysis and oxidation would presumably produce keto-aldehyde **108** and at this stage we could follow one of the methods already reported for the total synthesis of patchouli alcohol[24,25,29] and racemic norpatchoulenol.[30,38]



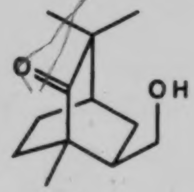
108

With these ideas in mind, we set out to oxidize diketone **101**, which was treated with m-chloroperbenzoic acid in dichloromethane solution in the presence of sodium bicarbonate. However, only the starting material was recovered even after extended reaction times at room temperature. Avoiding the use of sodium bicarbonate did not have any effect on the outcome of the reaction. The use of peroxytrifluoroacetic acid,[65] however, produced very good results;

compound **109** was obtained in essentially quantitative yield. The reaction was carried out in the presence of disodium hydrogen phosphate as a buffer, to avoid hydrolysis of the resulting acetate. The high resolution ^{1}H nmr spectrum of **109** showed signals for the two protons adjacent to the acetyl group at δ 4.04 and 3.84 each as a doublet of doublets. Also, the acetate peak was evident at δ 1.96.



109

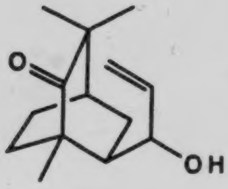


110

Hydrolysis of the acetyl group was achieved without difficulty in 92% yield by stirring a solution of compound **109** in methanol with a saturated aqueous solution of potassium carbonate at room temperature for three hours. The ^{1}H nmr spectrum of the resulting hydroxy-ketone (**110**) displayed a doublet with an integral of 2 at δ 3.54 and no signal for an acetyl group in the δ 2.0 region. Its mass spectrum was in agreement with a molecular formula of $C_{12}H_{20}O_2$, showing a molecular ion peak at m/z 196.1464.

After considerable experimentation, it was found that the best conditions for the oxidation of **110** to **108** required the use of a supported chromium reagent. In this regard, pyridinium dichromate, buffered or unbuffered pyridinium chlorochromate and Swern's reagent proved to be quite inefficient, producing complex mixtures that decomposed further very readily. Pyridinium chlorochromate adsorbed on Alumina[57] was the reagent of choice, affording keto-aldehyde **108** in *ca.* 86% yield. This compound turned out to be highly unstable and all purification attempts resulted in extensive decomposition. Therefore, the crude material was immediately utilized in the next reaction.

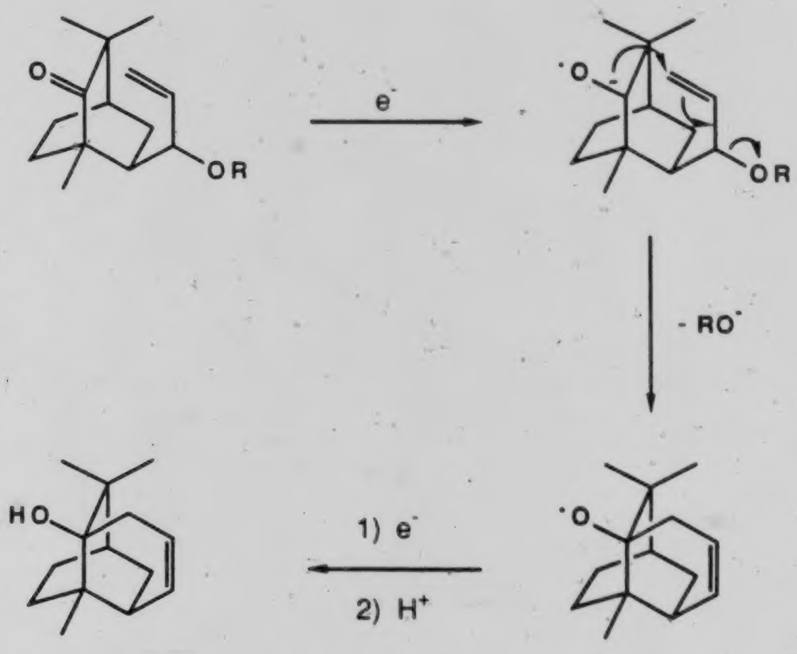
When **108** was exposed to the action of vinyllithium at low temperature, the allylic alcohol **111** was isolated in 87% yield. Compound **111** displayed vinylic proton signals at δ 5.80, 5.26 and 5.13 in its ^{1}H nmr spectrum. Moreover, a broad signal at δ 4.42, indicated the presence of a proton adjacent to an hydroxyl group. The high resolution mass spectrum showed a molecular ion peak at



111

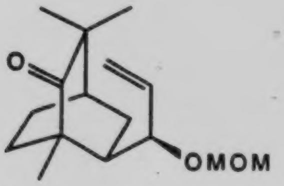
m/z 222.1619, in concord with the molecular formula $C_{14}H_{22}O_2$. The stereochemistry of the newly created chiral center was not known at this point, but the sharpness of the signals in the nmr spectrum suggested that a single isomer had been obtained. Quite unexpectedly, the ensuing reaction demonstrated the existence of two epimeric compounds.

With compound **111** in our hands, it was now necessary to convert the alcohol functionality into a leaving group that would allow a reductive cyclization reaction to take place:

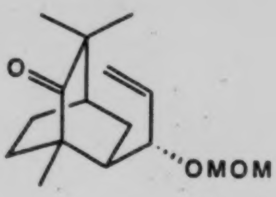


15

A methoxymethyl group bound to the oxygen has been used by Teisseire and coworkers in a number of opportunities[29,30,38] and we decided to follow the same approach. In contrast to the findings of Teisseire and his group, treatment of **111** with methoxymethyltriethylammonium chloride[30,66] in refluxing acetonitrile failed to give the corresponding MOM ether in several attempts. Deprotonation of the alcohol with lithium diisopropylamide followed by addition of chloro- or bromomethyl methyl ether was also unsuccessful. Nevertheless, when sodium hydride was used as the base, a 96% yield of a 2:1 mixture of the epimeric MOM ethers **112** and **113** was obtained.



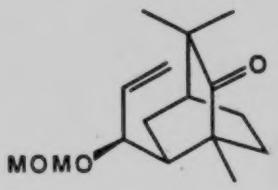
112



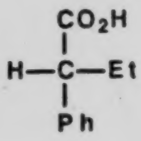
113

The ^{1}H nmr spectrum of each compound showed signals for three vinyl protons at δ 5.75-5.15 and singlets at δ 3.36 and 3.35, respectively, for the methoxy groups. The infrared spectra presented bands at 1718 and 1715 cm^{-1}, representing the ketone carbonyls, and the mass spectra displayed molecualr ion peaks at m/z 266.1885 and 266.1881, in accordance with the formula $C_{16}H_{26}O_3$.

The stereochemistry around the carbon atom bearing the MOM substituent could not be assigned unambiguously from the data supplied by nmr spectroscopy. Our assignment was made on the basis of the spectral data published by Teisseire *et al.* for compound **114**, which corresponds very closely to the results of our nmr experiments. The absolute stereochemistry of **114** was established by Teisseire using Horeau's method.[67-70] This consists of reacting an optically active secondary alcohol with an excess of racemic α-phenylbutyric anhydride. The alcohol reacts preferentially with one of the enantiomers of the reagent due to steric requirements. After isolation and hydrolysis of the unreacted anhydride, the optical activity of the resulting α-phenylbutyric acid is measured and a correlation is made using the following empirical rule: if the acid obtained is levorotatory (**115**), the stereochemistry of the secondary alcohol is such that, in a Fischer projection in which the hydroxyl

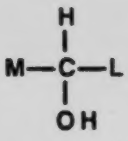


114



$$\begin{array}{c} CO_2H \\ | \\ H-C-Et \\ | \\ Ph \end{array}$$

115

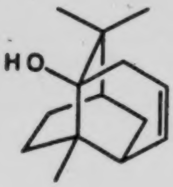


$$\begin{array}{c} H \\ | \\ M-C-L \\ | \\ OH \end{array}$$

116

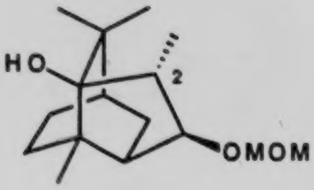
group and the hydrogen occupy the positions shown in **116**, the most sterically demanding group (**L**) is situated to the right.

Having obtained compounds **112** and **113**, it was time now to examine the reductive cyclization process. Treatment of **112** with sodium in refluxing tetrahydrofuran gave a mixture of three substances by TLC, which were separated by HPMPLC. The ^{1}H nmr spectrum of the faster moving compound displayed two doublets of doublets at δ 5.71 and 5.49, and singlets at δ 1.10 and 0.81. Its infrared spectrum showed bands at 3620 (free O-H), 3500 (bonded O-H) and 1620 cm^{-1} (C=C). The mass spectrum presented a molecular ion peak at m/z 206.1675, in accordance with the molecular formula $C_{14}H_{22}O$. These data are in full agreement with the structure of norpatchoulenol (**15**) and also with the data reported in the literature.[30] Unfortunately, the isolated yield of **15** was only 14%.



15

The other two substances obtained were identified as the five-membered ring cyclization products **117** and **118** in a 3:2 ratio. The yields were 46% and 27%, respectively. Compound **117** presented a doublet at δ 3.58, corresponding to the proton on the carbon atom bearing the ether substituent, a broad quintet at δ 2.79 for the proton on C-2 and a methyl doublet centered at δ 1.01. The molecular ion peak in its mass spectrum appeared at m/z 268.2038, in concord with the formula $C_{16}H_{28}O_3$. Compound **118** displayed comparable signals in its ^{1}H nmr spectrum at δ 3.39, 2.44 and 1.24, respectively, and a molecular ion peak at m/z 268.2040. The stereochemistry of the C-2 center was assigned on the basis of the following considerations. In the compound with the *cis*-arrangement, the methyl group is situated in between the oxygen atoms of the hydroxyl and ether groups and therefore it would be expected to appear at a lower field than in the case of the *trans*-stereochemistry. A comparable rationale holds for the methine proton at C-2. Thus, the substance showing the methyl signal at higher field and the methine proton at lower field was assigned structure **117**.



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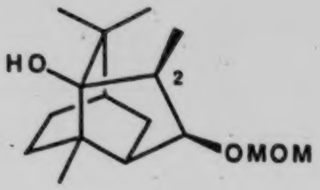
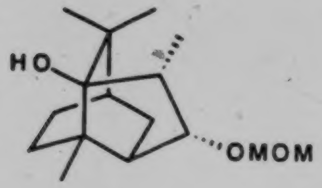


118

Analogous exposure of the other epimeric hydroxy-ether (**113**) gave similar results; norpatchoulenol was obtained in 9% yield, and compounds **119** and **120** in 41% and 21% yields.



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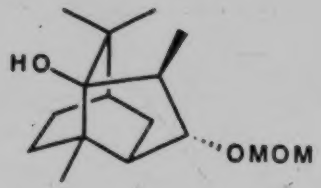
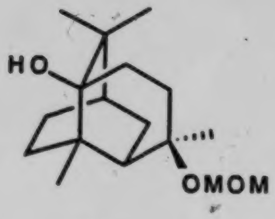
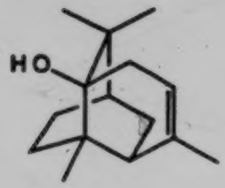


120

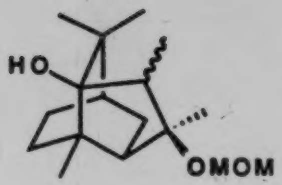
This is in contrast with the observations of Teisseire *et al.* in his synthesis of patchouli alcohol[29,30] (*vide supra*). When they subjected compound **47** to comparable conditions, **121** was obtained as a major product (64%) and the mixture of epimers **49** as a minor component. However, when **50** was used as the substrate, only the five-membered ring cyclization product was formed, in 70% yield.



47



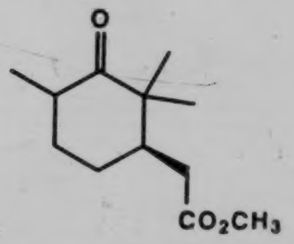
121



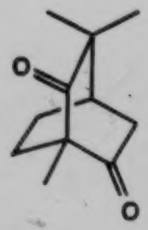
49

In an attempt to improve the yield of the reductive cyclization reaction, we decided to try a different reducing agent. Lanthanide derivatives such as samarium and ytterbium diiodides have been found to be powerful reducing agents, with the added advantage of being soluble in organic solvents, particularly in tetrahydrofuran.[76] More recently, samarium diiodide has been used for the intramolecular cyclization of 2-(ω–iodoalkyl)cycloalkanones in high yields.[77] However, treatment of the MOM-ether **112** with samarium diiodide in the presence of iron tris(dibenzoylmethane) [Fe(DBM)$_3$] led only to the recovery of the unchanged starting material.

While we were repeating the complete sequence of reactions to build up more material, we came across a result that suggested to us a different, more straightforward manner of converting the keto-ester **87** into the keto-aldehyde **108**. During the course of the methylation of compound **87** we isolated a product whose spectral features seemed to suggest the structure **122**. This compound would originate from an intramolecular Claisen condensation of the keto-ester **89**. The diketone **122** could presumably be converted into the enol-ether **123**, hydrolysis of which would give the desired keto-aldehyde **108**.

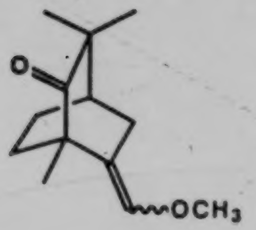


89



122

Towards this end, we attempted to carry out the cyclization of compound **89**. However, treatment of **89** with potassium hydride or potassium hexamethyldisilazide under various conditions failed to generate the desired compound. This is most likely due to the fact that the reaction is reversible, and compound **89** is probably thermodynamically more stable than **122**. What we needed then was a way of displacing the equilibrium towards the coveted diketone. Since **122** was to be converted into the keto-aldehyde **108** by means of a Wittig reaction, it occurred to us that the Wittig reagent could be used as the trapping agent during the Claisen condensation. If the less sterically hindered carbonyl group were to react selectively with the trapping substance, the enol-ether **123** would be obtained.



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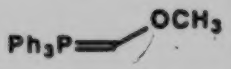
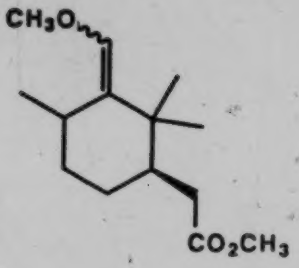


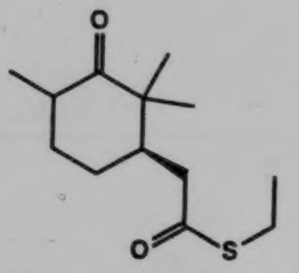
124

When the keto-ester **89** was reacted with the phosporous reagent **124** and an excess of potassium hydride, a 52% of the desired enol-ether was produced, as a 7:1 mixture of *cis-* and *trans* isomers. Unfortunately, the reaction proved not to be highly reproducible. In other instances lower yields of **123** were obtained, along with variable amounts of compound **125**, which resulted from the reaction of **89** with **124**. The mixture of isomeric enol-ethers showed resonances in the ^{1}H nmr spectrum at δ 5.87 and 5.82 for the vinylic protons and at δ 3.46 and 3.60 for the methoxy group. Its infrared spectrum presented bands at 1716 for the carbonyl group and at 1671 cm^{-1} for the double bond, and the mass spectrum displayed a molecular ion peak at m/z 208.1469, representing the formula $C_{13}H_{20}O_3$. In the case of **125**, the ^{1}H nmr had signals at δ 5.70 and 5.66 for the vinylic protons, and at δ 3.66, 3.65, 3.54 and 3.46 for the methoxy groups. Bands at 1731 and 1680 cm^{-1} were observed in the infrared spectrum for the carbonyl and double bond, respectively, and a molecular ion peak at m/z 240.1736 was in accordance with the molecular formula $C_{14}H_{24}O_3$.



125

It was necessary then to avoid, or at least minimize, the production of the undesired byproduct **125**. A way to realize that would be to decrease the residence time of **89** in the reaction mixture, that is, to accelerate its conversion into the diketone **122**. This could be achieved by replacing the methoxy group in **89** with a better leaving group. Along this line of reasoning, a thiol ester was deemed as a good candidate, as the sulfur would certainly augment the reactivity towards the cyclization. Thus, we set forth to prepare the required substrate **126**.



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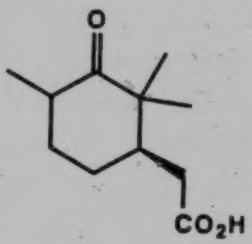
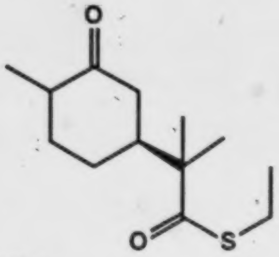


127

In this context, the keto-ester **89** was treated with an excess of lithium iodide in reluxing pyridine, in the presence of a small amount of water,[71] to give the carboxylic acid **127** in 88% yield. This compound presented a broad peak at δ 12-11 in the ^1H nmr spectrum, as well as signals in the δ 4.5-3.5 region. Its infrared spectrum showed bands at 3500-2600 cm^{-1} for the carboxylic OH group and at 1737 and 1706 cm^{-1} for the carbonyl groups. The mass spectrum was in accordance with the formula $C_{11}H_{18}O_2$, displaying the molecular ion at m/z 198.1253. The thiol ester **126** could then be formed as a 2:1 mixture of epimers, in quantitative yield, by treatment of **127** with phenyl dichlorophosphate and ethanethiol in the presence of pyridine.[72] The ^1H nmr spectrum of **126** presented a doublet of quartets at δ 4.68 for the methylene group adjacent to the sulfur atom, and triplets at δ 1.25 and 1.24 for the corresponding methyl groups. In the infrared spectrum there were bands at 1705 and 1687 cm^{-1} representing the two carbonyl groups, and the mass spectrum showed a molecular ion peak at m/z 242.1343, in agreement with the molecular formula $C_{13}H_{22}O_2S$.

Treatment of **126** with lithium diisopropylamide in tetrahydrofuran at -78°C produced a mixture of two major substances. After chromatographic separation, the faster moving component was isolated in 22% yield as a 1:1 mixture of epimers and tentatively assigned the structure **128**. The ^1H nmr of **128** displayed a quartet at δ 2.88 and triplets at δ 1.26 and 1.25, corresponding to the ethyl group, as well as methyl doublets at δ 0.88 and 0.87 and methyl singlets at δ 0.99 and 0.80. The infrared spectrum presented bands at 1736 and 1691 cm^{-1} for the two carbonyl groups. However, high resolution mass spectroscopy failed to show a molecular ion peak consistent with the molecular formula $C_{13}H_{22}SO_2$.

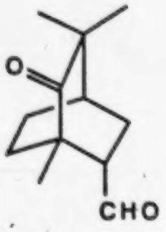


128

The diketone **122** was also obtained in 15% yield as a slower moving constituent of the mixture. Its ^1H nmr spectrum showed a quintet at δ 2.14, characteristic of the methine proton, as well as methyl groups at δ 1.29, 1.09 and 1.08. The ^{13}C nmr displayed two carbonyl groups at δ 213.0 and 208.4. Bands at 1736 and 1707 cm^{-1} in the infrared spectrum confirmed their existence. The mass spectrum presented a molecular ion peak at m/z 180.1150, in agreement with the formula $C_{11}H_{16}O_2$. The reaction was also carried out in 1,2-dimethoxyethane at -50°C, and using potassium hexamethyldisilazade in tetrahydrofuran or 1,2-dimethoxyethane with similar results.

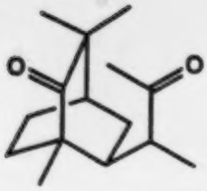
Since our attempts of base induced cyclization of the thiol ester **126** were somewhat discouraging due to the low yield of diketone **122**, we turned our attention to the possibility of effecting the desired reaction under acidic conditions. For this purpose we subjected the keto-acid **127** to the action of polyphosphoric acid and acetic acid at 100°C.[80,81] After workup and chromatography we were able to isolate the diketone **122** in 25% yield. A second product was also obtained that appears to be isomeric with **122**. This substance shows methyl singlets at δ 1.18 and 0.57 and a methyl doublet at δ 0.92 in the ^{1}H nmr spectrum. Also a triplet at δ 5.70 and a doublet at δ 4.44 suggest the presence of a disubstituted double bond. The infrared spectrum spectrum displayed intense bands at 1810, 1735 (broad) and 1644 cm^{-1}, and its mass spectrum presented a molecular ion peak at m/z 180.1150, in accordance with the molecular formula $C_{11}H_{16}O_2$. More extensive NMR experiments are currently under progress to elucidate the structure of this substance.

The enol-ether **123** was hydrolyzed to a chromatographically separable mixture of the aldehyde **108** and its corresponding epimer **129**, in a 2:1 ratio, by treatment with 35% perchloric acid solution. The ^{1}H nmr spectrum of **108** showed a doublet at δ 9.49 for the aldehydic proton and singlets at δ 1.15, 1.11 and 1.06 for the methyl groups. Its infrared spectrum presented bands at 2720 (aldehyde C-H) and 1720 cm^{-1} (C=O), and the mass spectrum displayed a molecular ion peak at m/z 194.1303, in accordance with the formula $C_{12}H_{18}O_2$. The aldehyde **129**, on the other hand, showed the aldehydic proton as a doublet at δ 9.87, and two signals for the methyl groups at δ 1.06 and 1.08 with a total integral of 9. Bands at 2740 and 1720 cm^{-1} in the infrared spectrum confirmed the presence of the aldehyde group, and a molecular ion peak at m/z 194.1305 in the mass spectrum was in agreement with the formula $C_{12}H_{18}O_2$. Assignment of the stereochemistry of the carbon atom bearing the aldehyde function was done by comparison with the reported[30] spectral data for these substances. Teisseire and coworkers[30] have described the epimerization of **129** by means of a deprotonation-kinetic protonation sequence (*vide supra*).

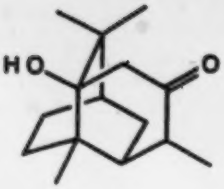


129

After the completion of the work described above, we were informed that the cyclization of the diketone **130** to the hydroxyketone **131** has been carried out.[78] The transformation was effected by treatment of **130** with lithium diisopropylamide in the presence of 2,2'-bipyridine at 0°C for 5 hours, to give a 75% yield of **131**.

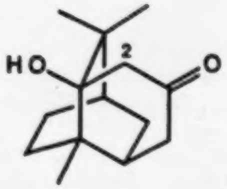


130



131

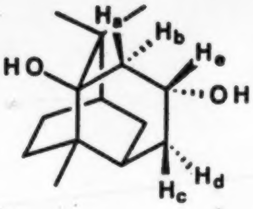
Undoubtedly, we tried this procedure on our diketone **101**. When the reaction was carried out with 4 equivalents of LDA at 0°C, no product formation was observed after 6 hours. Warming up the reaction mixture to room temperature, however, led to the isolation of the expected product **76** in 38% yield, based on the consumed starting material, 53% of which was recovered. Increasing the amount of the base to 7 equivalents and the reaction time to 5 days improved the yield of **76** to 59%, with 49% recovery of the starting material.



76

Compound **76** showed a band for the hydroxyl group at 3514 cm^{-1} and an intense absorption for the carbonyl group at 1702 cm^{-1} in the infrared spectrum. The high resolution mass spectrum displayed a molecular ion peak at m/z 222.1619, in accordance with the formula $C_{14}H_{22}O_2$. Its ^1H nmr spectrum presented only three methyl singlets, at δ 1.11, 1.03 and 0.95 and signals at δ 2.74 and 2.38 for the protons on C-2. Moreover, only one carbonyl group was observed in the ^{13}C nmr spectrum at δ 211.4 and a signal at δ 77.8 confirmed the presence of the carbon atom bearing the hydroxyl group.

With compound **76** in our possession we had achieved the construction of the complete carbon skeleton of norpatchoulenol. All there was left to do was the transformation of the carbonyl group into a double bond at the proper position. Towards this end we treated the hydroxy-ketone **76** with sodium borohydride in ethanol, to produce the diol **132** in quantitative yield. Its ^1H nmr spectrum showed the proton adjacent to the hydroxyl group as a triplet at δ 4.30. The simplicity of the splitting pattern of this signal could presumably be attributed to very small coupling constants with two of the vicinal protons. This conjecture is supported by the results of molecular mechanics (MMPM) calculations, which show dihedral angles of -82° and 84° between H_e and each of H_b and H_d, respectively. The stereochemistry around the carbon atom bearing the secondary hydroxyl group, as depicted in **132**, rests on the assumption that the reducing agent would attack from the less sterically crowded face of the carbonyl group. The structure of **132** was also confirmed by the absence of bands in the carbonyl regions of the infrared and ^{13}C nmr spectra, and by the presence of a molecular ion peak at m/z 244.1762 in its high resolution mass spectrum.



132

Further investigations are being carried out towards the dehydration of the diol **132** to produce norpatchoulenol.

Experimental.

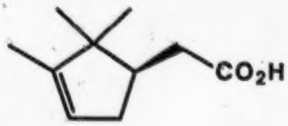
General.

Melting points were recorded on a Köfler hot stage apparatus and are uncorrected. Infrared spectra (ir) were determined using the following spectrophotometers: Perkin-Elmer model 457, model 297, Nicolet 7199 FTIR and Nicolet MX-1 FTIR. Mass spectra (ms) were obtained using an Kratos AEI MS50 high resolution mass spectrometer and low resolution spectra on a Kratos AEI MS12 spectrometer. Gas chromatographic analyses were performed on a Hewlett-Packard 5750 instrument equipped with a flame ionization detector, using columns of 15% SE-30, 15% OV-17 or 15% OV-1 on Chromosorb W, with helium as the carrier gas. Elemental analyses were determined by the microanalytical laboratory of this department. Samples were routinely distilled prior to the analysis. High Performance Medium Pressure Liquid Chromatography (HPMPLC) was carried out on ACE Glass Inc. Michel-Miller equipment, using a solvent pump from Fluid Metering Inc. Proton nuclear magnetic resonance spectra (^{1}H nmr) were obtained using the following spectrometers: Varian EM-360 (60 MHz), Bruker WP-80 (80 MHz), Bruker WH-200 (200 MHz), Bruker WH-400 (400 MHz) and Bruker AM-400 (400 MHz). Coupling constants are reported to within ±0.5 Hz. Carbon-13 nuclear magnetic resonance spectra (^{13}C nmr) were recorded on a Bruker WH-200 (50.3 MHz), Bruker WH-400 (100.6 MHz) and Bruker AM-400 (100.6 MHz). Carbon-13 multiplicities were derived from off-resonance or Carr-Purcel-Meiboom-Gill spin echo J-modulated experiments (APT or Attached Proton Test).[73,74] Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuteriochloroform signal, whereas methylene groups, quaternary carbon atoms and carbonyl groups appear in phase (p) with it. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer-substracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing an antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with helium gas for 5-10 min. prior to use. Two dimensional (2D) homonuclear and heteronuclear correlation spectra (COSY and HCCORR) experiments were performed using the BRUKER DISNMR software package. For the COSY sequence, normally 16 scans per FID were accumulated to fulfill the 16-transient phase program, which provided quadrature detection in F1. Generally 1K × 128 words or 1K × 256 words were acquired and were zero-filled to 256 and 512 points in F1, respectively, during Fourier transformation. Sine-bell digital apodization applied in both dimensions gave the best resolved spectra. A Bruker data station equiped with an ASPECT 1000 computer (256K), array processor, graphics display processor and digital plotter was used for transforming and plotting 2D data matrices. Optical rotations were determined in a Perkin-Elmer 241 polarimeter. The solvents used for this purpose were purified as described below. Ozone was generated using a Welsbach ozonator (80 V). All isolated products were found to be at least 95% pure, as determined by tlc and NMR.

Materials.

Flash chromatography was performed according to the procedure of Still using silica gel of 230-400 mesh. HPMPLC was carried out on colums filled with silica gel H for thin layer chromatography. Dry column flash chromatography[79] was conducted on silica gel of 200-450 mesh. Thin layer chromatography was performed on Merck aluminum-backed plates precoated with silica gel 60 GF_{254}. Solvents were purified as follows: ethyl ether, tetrahydrofuran (THF) and dimethoxyethane (DME) by distillation from a blue or purple solution of sodium benzophenone ketyl under an argon atmosphere; dimethyl sulfoxide (DMSO) and benzene by distillation over calcium hydride at reduced and atmospheric pressure, respectively; triethylamine, diisopropylamine and pyridine by distillation first over potassium hydroxide and then over calcium hydride; methylene chloride by distillation over phosphorous pentoxide.

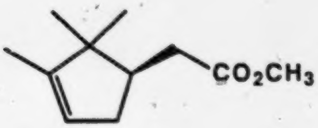
(S)-(+)-α-Campholenic acid (81).



(+)-10-camphorsulfonic acid (**78**) (100 g, 0.39 mol) was added in portions, with continuous stirring, over a 30 min. period, to molten potassium hydroxide (120 g of 85% material, 1.82 mol, 4.67 eq) contained in a porcelain dish. After the addition was complete, the dark mixture was heated with a Bunsen burner for an additional 20 min. and then cooled to room temperature. The brown solid was dissolved in water (900 mL). The solution was then extracted with ether (3 × 150 mL). The ether extracts were discarded. Ice-cold aqueous HCl was added cautiously to the aqueous solution until pH 1. The solution was then extracted with methylene chloride (4 × 150 mL). The combined organic extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), filtered and concentrated to leave a brown viscous liquid which was purified by bulb to bulb distillation (130-160°C/6.5 torr) to provide (+)-α-campholenic acid (**81**) (50.1 g, 80%) as a colorless viscous liquid: $[\alpha]_D^{22}$ +9.2° (c = 0.98, $CHCl_3$); ^1H nmr (400 MHz, $CDCl_3$) δ 5.23 (br. s, 1H, =CH-), 2.48 (dd, 1H, J = 3, J' = 14 Hz,

-C**H**HCO-), 2.43 (m, 1H, -C**H**HCH=), 2.35-2.15 (m, 2H, -CH**H**CO- and -CH**H**CH=), 1.94 (m, 1H, $-CH_2\mathbf{CH}CH_2-$), 1.61 (m, 3H, $=C\mathbf{H_3}$), 1.03 (s, 3H, $-C\mathbf{H_3}$) and 0.82 (s, 3H, $-C\mathbf{H_3}$); ^{13}C nmr (100 MHz, $CDCl_3$) δ 180.2 (p), 147.6 (p), 121.6 (a), 46.7 (p), 46.1 (a), 35.5 (p), 35.1 (p), 25.4 (a), 19.6 (a), 12.3 (a); ir (neat) 3500-2300 (CO_2H), 1705 (C=O) and 1370 cm^{-1} (gem CH_3); ms M^+ 168.1148 (calcd. for $C_{10}H_{16}O_2$: 168.1150). Anal. calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; found: C, 71.67; H, 9.72.

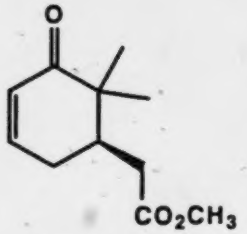
(S)-(+)-Methyl α-campholenate (82).



A mixture of (+)-α-campholenic acid (**81**) (50.1 g, 0.30 mol) and anhydrous potassium carbonate (103 g, 0.75 mol, 2.5 eq) in acetone (400 mL) was stirred for 2 hrs. at room temperature under argon atmosphere. Methyl iodide (93 mL, 211.4 g, 1.49 mol, 5.0 eq) was added and the reaction mixture was stirred overnight at room temperature. The suspension was filtered and the residue washed thoroughly with acetone. The combined organic extracts were then concentrated under reduced pressure. Short path distillation of the residue under reduced pressure afforded (+)-α-methyl campholenate (**82**) (54.4 g, 98%) as a colorless liquid: b.p. 75-80°C/3 torr; $[\alpha]_D^{22}$ +12.0° (c = 1.18,

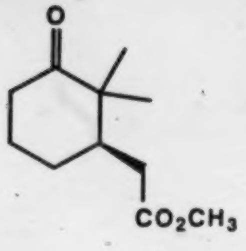
$CHCl_3$); ^1H nmr (400 MHz, $CDCl_3$) δ 5.23 (br. s, 1H, =C**H**-), 3.67 (s, 3H, -OC**H**$_3$), 2.40 (d, 1H, *J* = 10 Hz, -C**H**HCO-), 2.33 (m, 1H, -C**H**HCH=), 2.25-2.15 (m, 2H, -CH**H**CO- and -CH**H**CH=), 1.87 (m, 1H, -CH$_2$C**H**CH$_2$-), 1.65 (m, 1H, =CC**H**$_3$), 1.00 (s, 3H, -C**H**$_3$) and 0.78 (s, 3H, -C**H**$_3$); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 174.1, 147.8, 121.5, 51.3, 46.7, 46.3, 35.5, 35.1, 25.4, 19.7 and 12.5; ir (neat) 3050 (C=CH) and 1740 cm^{-1} (ester C=O); ms M^+ 182.1303 (calcd. for $C_{11}H_{18}O_2$: 182.1307).

(R)-(+)-5-Carbomethoxymethyl-6,6-dimethyl-2-cyclohexenone (86).

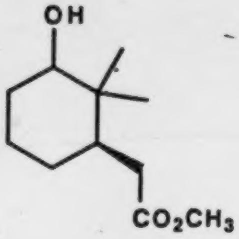


At -78°C ozone was passed through a solution of (+)-methyl α-campholenate (**82**) (38.1 g, 0.20 mole) in CH_2Cl_2-CH_3OH (1:1, 100 mL) until a light blue color was retained (ca. 5 hrs.). At this point oxygen was bubbled through to expel the excess of ozone. A solution of triphenylphosphine (58.0 g, 0.22 mole, 1.1 eq) in methylene chloride (100 mL) was then added slowly. After the addition was complete, the cryogenic bath was removed and the mixture stirred at room temperature for additional 11 hrs. under argon atmosphere. The solvents were evaporated under reduced pressure and the residue was dissolved in benzene (150 mL). p-Toluenesulfonic acid monohydrate (3.80 g, 20 mmol, 0.1 eq) was added and the mixture was refluxed for 6 hrs. with continuous removal of water (Dean-Stark). The solvent was then evaporated *in vacuo* and ether (100 mL) was added to precipitate the triphenylphosphine oxide. The suspension was then filtered and the residue was washed thoroughly with ether. The combined ethereal solutions were dried (Na_2SO_4), filtered and concentrated. Bulb to bulb distillation of the residue (140-160°C/3.3 torr) provided the desired unsaturated keto-ester **86** (31.9 g, 80%) as a slightly yellowish oil: $[\alpha]_D^{22}$ +58.0° (c = 0.94, $CHCl_3$); ^1H nmr (400 MHz, $CDCl_3$) δ 6.83 (ddd, 1H, J = 10, J' = 7, J' = 5 Hz, -C**H**=CHCO-), 5.97 (ddd, 1H, J = 10, J' = 2.0, J' = 2.0 Hz, -CH=C**H**CO-), 3.70 (s, 3H, -OC**H**$_3$), 2.55 (dd, 1H, J = 3.5, J' = 15 Hz, -C**H**HCO-), 2.53 (m, 1H, =CH-C**H**H-), 2.41 (m, 1H, =C-CH**H**-), 2.24 (dd, 1H, J = 10, J' = 15 Hz, -CH**H**CO-), 2.19 (m, 1H, -CH_2-C**H**-CH_2-), 1.18 (s, 3H, -C**H**$_3$) and 1.01 (s, 3H, -C**H**$_3$); ^{13}C nmr (100 MHz, $CDCl_3$) δ 202.4 (p), 172.4 (p), 146.1 (a), 127.7 (a), 51.0 (a), 44.5 (p), 40.1 (a), 34.5 (p), 28.8 (p), 22.0 (a) and 18.6 (a); ir (neat) 1730 (ester C=O) and 1670 cm^{-1} (C=C); ms M^+ 196.1098 (calcd. for $C_{11}H_{16}O_3$: 196.1100). Anal. calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; found: C, 67.14; H, 8.28.

Hydrogenation of 86 using PtO_2 as catalyst.



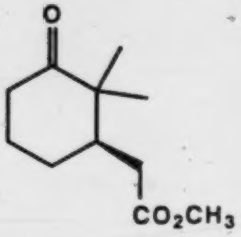
87



88

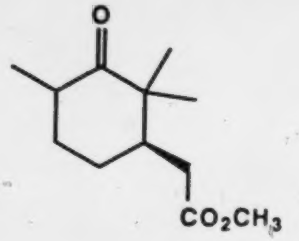
A solution of the unsaturated keto-ester **86** (3.8 g, 19 mmol) in ethyl acetate (15 mL) was subjected to hydrogenation in a Parr apparatus at 10-20 psig, using platinum dioxide (0.25 g) as catalyst. The mixture was then filtered through a sintered glass funnel and concentrated. Flash chromatography of the residue (20% ethyl acetate in hexane) afforded the keto-ester **87** (3.05 g, 80%): ^{1}H nmr (200 MHz, $CDCl_3$) δ 3.68 (s, 3H, -OC**H**$_3$), 1.13 (s, 3H, -C**H**$_3$), 1.03 (s, 3H, -C**H**$_3$); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 214.3, 173.1, 51.4, 48.1, 44.0, 37.5, 35.2, 26.8, 24.5, 22.7 and 19.8; ir (neat) 1740 (ester C=O) and 1710 cm^{-1} (C=O); ms M$^+$ 198.1255 (calcd. for $C_{11}H_{18}O_3$: 198.1256). Anal. calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; found: C, 66.45; H, 9.17. Continued elution gave the hydroxy-ester **88** (0.37 g, 9%): ^{1}H nmr (80 MHz, $CDCl_3$) δ 3.85 (s, 3H, -OC**H**$_3$), 3.30 (complex, 1H, -C**H**-OH), 2.50 (dd, 1H, J = 3, J' = 14 Hz, -C**H**H-CO_2CH_3), 1.03 (s, 3H, -C**H**$_3$), 0.75 (s, 3H, -C**H**$_3$); ir (neat) 3650-3200 (OH), 1735 cm^{-1} (C=O); ms M$^+$ 200.1415 (calcd. for $C_{11}H_{20}O_3$: 200.1412).

(R)-(+)-3-Carbomethoxymethyl-2,2-dimethylcyclohexanone (87).

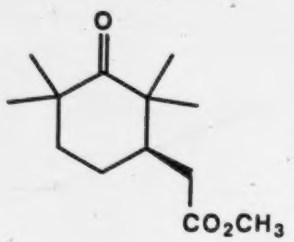


A solution of the unsaturated keto-ester **86** (20.2 g, 0.103 mole) in ethyl acetate (100 mL) was subjected to hydrogenation in a Parr apparatus at 10-20 psig, using 5% palladium over carbon as catalyst. When hydrogen take-up ceased, the mixture was filtered through a sintered glass funnel. The solution was then concentrated to yield the desired keto-ester **87** (19.8 g, 97%): $[\alpha]_D^{22}$ +55.5° (c = 0.95, CHCl$_3$); ^{1}H nmr (400 MHz, CDCl$_3$) δ 3.68 (s, 3H, -OC**H**$_3$), 2.8-2.5 (m, 2H), 2.48 (m, 2H, -CH$_2$-C**H**$_2$-CO-), 2.34 (dddd, 1H, J = 1.5, J' = J'' = 4.5, J''' = 14 Hz, -C**H**H-CO$_2$CH$_3$), 2.17 (dd, 1H, J = 10, J' = 14 Hz, -CH**H**CO$_2$CH$_3$), 2.10 (dddd, 1H, J = J' = 3.5, J'' = J''' = 10 Hz), 1.98 (m, 1H), 1.85 (m, 1H), 1.13 (s, 3H, -C**H**$_3$) and 1.03 (s, 3H, -C**H**$_3$); ^{13}C nmr (50.3 MHz, CDCl$_3$) δ 214.3, 173.1, 51.4, 48.1, 44.0, 37.5, 35.3, 26.8, 24.5, 22.7 and 19.8; ir (neat) 1740 (ester C=O) and 1710 cm^{-1} (C=O); ms M$^+$ 198.1255 (calcd. for $C_{11}H_{18}O_3$: 198.1251). Anal. calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; found: C, 66.45; H, 9.17.

(3R, 6R)- and (3R, 6S)-3-Carbomethoxymethyl-2,2,6-trimethylcyclohexanone (89) and (R)-3-Carbomethoxymethyl-2,2,6,6-tetramethylcyclohexanone (90).



89

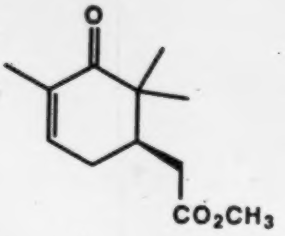


90

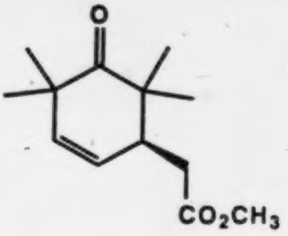
Potassium hydride (6.20 g of 35% material, 54.1 mmol, 1.07 eq) contained in a three-necked flask was washed with dry tetrahydrofuran (4 × 15 mL). The white residue was suspended in dry tetrahydrofuran (100 mL) and hexamethyldisilazane (21.5 mL, 16.45 g, 102 mmol, 2.02 eq.) was added dropwise. Upon completion of the addition, the mixture was stirred at room temperature for 30 min. Then the reaction mixture was cooled to -78°C and a solution of the keto-ester **86** (10.0 g, 50.4 mmol) in tetrahydrofuran (150 mL) was added dropwise. The mixture was then stirred at -78°C for additional 30 min., after which methyl iodide (16 mL, 36.5 g, 0.26 mmol, 5.1 eq) was added at once. The mixture was stirred at -78°C for ca. 16 hrs. and then the reaction was quenched by addition of saturated aqueous ammonium chloride (100 mL). The resulting layers were separated and the aqueous phase was extracted with ethyl ether

(4 × 100 mL). The mixed organic extracts were washed in turn with 50% sodium thiosulfate (50 mL), water (2 × 50 mL) and brine (100 mL), and then dried (Na_2SO_4), filtered and concentrated. HPMPLC of the residue (5% ethyl acetate in petroleum ether) gave the tetramethyl keto-ester **90** (0.69 g, 6% yield): ^{1}H nmr (400 MHz, $CDCl_3$) δ 3.69 (s, 3H, -OC**H**$_3$), 2.45 (dd, 1H, J = 14, J' = 3 Hz, -C**H**$_2$CO-), 2.22-2.07 (m, 2H), 1.78-1.61 (m, 3H), 1.15 (s, 3H, -C**H**$_3$), 1.14 (s, 3H, -C**H**$_3$), 1.10 (s, 3H, -C**H**$_3$) and 1.02 (s, 3H, -C**H**$_3$); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 219.0, 173.3, 51.4, 47.6, 43.8, 43.1, 37.7, 35.9, 27.8, 27.2, 24.7, 23.7 and 21.8; ir (neat) 1730 (ester C=O) and 1700 cm^{-1} (ketone C=O); ms M$^+$ 226.1570 (calcd. for $C_{13}H_{22}O_3$: 226.1570). Anal. calcd. for $C_{13}H_{22}O_3$: C, 68.99, H, 9.80; found: C, 69.29, H, 9.86). Continued elution gave the trimethyl keto-ester **89** (8.85 g, 77% yield) as a 2:1 mixture of epimers (det. by nmr). The ^{1}H nmr spectrum (400 MHz, $CDCl_3$) exhibited two sets of signals. The following ^{1}H nmr data were attributed to the major isomer: δ 3.68 (s, 3H, -OC**H**$_3$), 2.65 (m, 1H, -C**H**(CH$_3$)CO), 1.09 (s, 3H, -C**H**$_3$) , 1.04 (s, 3H, -C**H**$_3$) and 0.999 (d, 3H, J = 7 Hz, -CH-C**H**$_3$). The following ^{1}H nmr data were attributed to the minor isomer: δ 3.67 (s, 3H, -OC**H**$_3$), 2.75 (m, 1H, -C**H**(CH$_3$)CO), 1.29 (s, 3H, -C**H**$_3$), 1.03 (s, 3H, -C**H**$_3$) and 0.996 (d, 3H, J = 7 Hz, -CH-C**H**$_3$). The following spectral data were recorded for the mixture: ir (neat) 1730 (ester C=O) and 1700 cm^{-1} (ketone C=O); ms M$^+$ 212.1412 (calcd. for $C_{12}H_{20}O_3$: 212.1413).

Methylation of the α,β-unsaturated keto-ester 86.



91

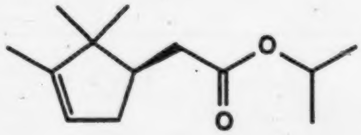


92

Sodium hydride (140 mg of 50% material, 2.9 mmol, 1.4 eq.) contained in a three-necked flask was washed with dry tetrahydrofuran (4 × 1 mL). The white residue was then suspended in tetrahydrofuran (3 mL) and a solution of the unsaturated keto-ester **86** (485 mg, 2.2 mmol) was added *via* syringe. The mixture was stirred for 15 min. at room temperature and then methyl iodide (0.16 mL, 0.36 g, 2.6 mmol, 1.2 eq.) was added. Stirring was continued for 4 hrs. and then the reaction was quenched by addition of water. The resulting layers were separated and the aqueous phase was further extracted with methylene chloride (3 × 5 mL). The combined organic extracts were washed with aqueous 5% hydrochloric acid (2 mL), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (5% ethyl acetate in petroleum ether) gave the unsaturated tetramethyl keto-ester **92** (81 mg, 13%): ^{1}H nmr (200 MHz, $CDCl_3$) δ 5.68 (m, 2H, -**CH**=**CH**-), 3.70 (s, 3H, -OCH_3), 2.77 (ddd, 1H, $J = J' = 4.5$, $J'' = 11$ Hz, -**CH**-CH_2), 2.53 (dd, 1H,

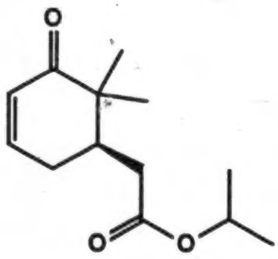
J = 4.5, J' = 16 Hz, -C**H**H-), 2.09 (dd, 1H, J = 11, J' = 16 Hz, -CH**H**-), 1.24 (s, 3H, -C**H**$_3$), 1.17 (s, 3H, -C**H**$_3$), 1.16 (s, 3H, -C**H**$_3$) and 1.06 (s, 3H, -C**H**$_3$); ir (CHCl$_3$ cast) 1740 (ester C=O) and 1710 cm^{-1} (ketone C=O); ms M$^+$ 224.1412 (calcd. for $C_{13}H_{20}O_3$: 224.1412); ^{13}C nmr (50.3 MHz, CDCl$_3$) δ 218.2, 172.7, 135.9, 126.4, 51.6, 46.9, 43.8, 42.7, 36.6, 27.4, 27.0, 25.2, 20.9. Continued elution gave the unsaturated trimethyl keto-ester **91** (36 mg, 8%): ^{1}H nmr (200 MHz, CDCl$_3$) δ 6.58 (m, 1H, =C**H**-), 3.69 (s, 3H, -OC**H**$_3$), 2.60-2.00 (m, 4H), 1.77 (br. s, 3H, C**H**$_3$-C=), 1.23 (m, 1H), 1.18 (s, 3H, -C**H**$_3$) and 0.98 (s, 3H, -C**H**$_3$); ir (neat) 1740 (C=O), and 1670 cm^{-1} (C=C); ms M$^+$ 210.1256 (calcd. for $C_{12}H_{18}O_3$: 210.1256).

(±)-Isopropyl α-campholenate.



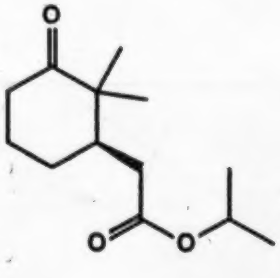
A mixture of (±)-α-campholenic acid (**81**) (4.0 g, 23.8 mmol) and anhydrous potassium carbonate (8.3 g, 60 mmol, 2.5 eq.) in acetone (50 mL) was stirred for 1 hr. at room temperature. Isopropyl iodide (4.8 mL, 8.2 g, 48 mmol, 2.0 eq.) was added and the reaction mixture was refluxed for 20 hrs. The mixture was then concentrated and the residue was dissolved in a mixture of methylene chloride and water (1:1, 100 mL). The layers were separated and the aqueous portion was further extracted with methylene chloride (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Bulb to bulb distillation of the residue afforded (±)-isopropyl α-campholenate (4.8 g, 97%) as a clear liquid: ^1H nmr (80 MHz, $CDCl_3$) δ 5.25 (br., 1H, =**CH**-), 5.00 (m, 1H, -**CH**(CH_3)$_2$), 1.63 (br. s, 3H, =C-**CH**$_3$), 1.12 (d, 6H, -CH(**CH**$_3$)$_2$), 1.00 (s, 3H, -**CH**$_3$) and 0.80 (s, 3H, -**CH**$_3$); ir (neat) 3070 (C=CH) and 1740 cm^{-1} (ester C=O); ms M^+ 210.1625 (calcd. for $C_{13}H_{22}O_2$: 210.1621).

(±)-5-Carboisopropoxymethyl-6,6-dimethyl-2-cyclohexenone.



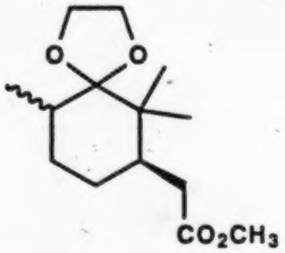
At -78°C ozone was passed through a solution of (±)-isopropyl α-campholenate (4.70 g, 22.4 mmol) in CH_2Cl_2-CH_3OH (1:1, 30 mL), until a light blue color was retained (ca. 90 min.). After bubbling oxygen through the mixture to expel the excess of ozone, a solution of triphenylphosphine (6.45 g, 24.6 mmol, 1.1 eq.) in methylene chloride (10 mL) was added slowly. After completion of the addition the mixture was stirred at room temperature for 12 hrs. The solution was then concentrated and the residue was dissolved in benzene (150 mL). p-Toluenesulfonic acid monohydrate (0.43 g, 2.2 mmol, 0.1 eq) was added and the reaction mixture was refluxed for 6.5 hrs. with continuous displacement of water (Dean-Stark). After removal of the solvent under reduced pressure, ethyl ether (100 mL) was added to precipitate the triphenylphosphine oxide. The suspension was then filtered and the residue was washed thoroughly with ether. The combined ethereal solutions were concentrated and bulb to bulb distillation of the residue (80-90°C/1.0 torr) gave the unsaturated keto-ester (4.0 g, 80%) as a clear liquid: ^{1}H nmr (200 MHz, $CDCl_3$) δ 6.83 (ddd, 1H, $J = 5$, $J' = 2$, $J'' = 1.5$ Hz, -**C*H***=CHCO-), 4.96 (m, 1H, =C**H**CO-), 4.03 (m, 1H, -C**H**$(CH_3)_2$), 1.25 (d, 3H, $J = 4$ Hz, C**H**$_3$-CH-CH_3), 1.24, (d, 3H, $J = 4$ Hz, CH_3-CH-C**H**$_3$), 1.16 (s, 3H, -C**H**$_3$), and 0.99 (s, 3H, -C**H**$_3$); ir (neat) 3050 (C=CH), 1730 (ester C=O) and 1680 cm^{-1} (C=C).

(±)-3-Carboisopropoxymethyl-2,2-dimethylcyclohexanone (94).



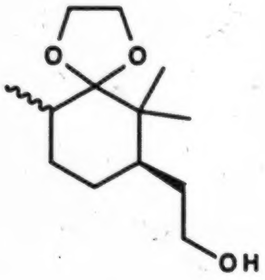
A solution of (±)-5-carboisopropoxymethyl-6,6-dimethylcyclohexen-2-one (3.8 g, 16.8 mmol) in ethyl acetate (25 mL) was subjected to hydrogenation in a Parr apparatus at 10-15 psig for 90 min, using 5% palladium over carbon as catalyst. The mixture was then filtered through sintered glass and concentrated. Bulb to bulb distillation of the residue (80-90°C/1.0 torr) gave the keto-ester **94** (3.7 g, 96%) as a clear liquid: ^{1}H nmr (80 MHz, $CDCl_3$) δ 5.02 (m, 1H, -C**H**$(CH_3)_2$), 1.25 (d, 6H, J = 4 Hz, -CH(C**H**$_3)_2$), 1.17 (s, 3H, -C**H**$_3$) and 1.12 (s, 3H, -C**H**$_3$); ir (neat) 1720 cm^{-1} (broad, C=O); ms M$^+$ 226.1574 (calcd. for $C_{13}H_{22}O_3$: 226.1570).

(3R, 6R)- and (3R, 6S)-3-Carbomethoxymethyl-1,1-ethylenedioxy-2,2,6-trimethylcyclohexane (95).



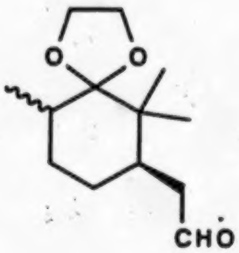
A mixture of the keto-ester **89** (2.66 g, 12.5 mmol), p-toluenesulfonic acid monohydrate (240 mg, 1.26 mmol, 0.1 eq) and ethylene glycol (10 mL, 11.1 g, 0.18 mol, 14.3 eq) in benzene (50 mL) was refluxed for 41 hrs. with displacement of water (Dean-Stark). After evaporation of the solvent *in vacuo*, the residue was dissolved in ether (50 mL) and the solution was extracted with 5% sodium bicarbonate. Drying (K_2CO_3), filtration and concentration gave the ketal-esters (**95**) as a 2:1 mixture of epimers, as determined by ^{1}H nmr (3.21 g, 100%): ^{1}H nmr (200 MHz, $CDCl_3$) δ 3.98 (m, 4H, -OC**H**$_2$C**H**$_2$O-), 3.65 (s, 3H, -OC**H**$_3$), 2.57 (m, 1H, -C**H**HCO-), 2.44 (dd, 1H, J = 3, J' = 14 Hz, -CH**H**CO-), 1.12 and 0.87 (each br. s, total 6H, 2 × -C**H**$_3$), 0.82 and 0.81 (each d, total 3H, J = 7 Hz, -CH-C**H**$_3$); ir (neat) 1740 cm^{-1} (C=O); ms M$^+$ 256.1680 (calcd. for $C_{14}H_{24}O_4$: 256.1675).

(3R, 6R)- and (3R, 6S)-1,1-ethylenedioxy-3-(2-hydroxyethyl)-2,2,6-trimethylcyclohexanone (96).



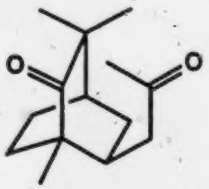
A solution of ketal-ester **95** (3.21 g, 12.5 mmol) in dry ether (20 mL) was added slowly to a suspension of lithium aluminum hydride (1.26 g, 33.2 mmol, 10.6 eq) in dry ether (20 mL). After completion of the addition, the mixture was refluxed for 20 hrs. The reaction was then quenched with water and acidified to pH 2 with aqueous 5% hydrochloric acid. The ethereal layer was separated and the aqueous layer further extracted with methylene chloride (3 × 10 mL). The combined organic extracts were washed with aqueous 5% sodium bicarbonate, dried (K_2CO_3), filtered and concentrated to yield the hydroxy-ketals **96** (2.68 g, 94%) as a viscous oil (mixture of epimers in a 2:1 ratio, det. by nmr): ^{1}H nmr (400 MHz, $CDCl_3$) δ 3.99 (m, 4H, $-OC\mathbf{H}_2C\mathbf{H}_2O-$), 3.62 (m, 2H, $-C\mathbf{H}_2OH$) 1.08, 0.90, 0.89, 0.87 (all s, total 6H, 2 × $-C\mathbf{H}_3$), 0.85 and 0.81 (d, total 3H, J = 7 Hz, $-CH-C\mathbf{H}_3$); ir (neat) 3380 (OH) and 1060 cm^{-1} (C-O); ms M^+ 228.1726 (calcd. for $C_{13}H_{24}O_3$: 228.1726).

(3R, 6R)- and (3R, 6S)-1,1-ethylenedioxy-3-(2-oxoethyl)-2,2,6-trimethylcyclohexanone (98).

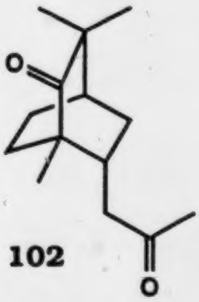


A mixture of the hydroxy-ketal **96** (1.19 g, 5.2 mmol), pyridinium chlorochromate (1.74 g, 8.1 mmol, 1.5 eq) and sodium acetate (135 mg, 1.6 mmol, 0.3 eq) in methylene chloride (10 mL) was stirred at room temperature for 2 hrs. Filtration of the mixture through consecutive layers of silica gel and basic alumina afforded the crude ketal-aldehydes **98** (932 mg, 79%) as a 2:1 mixture of epimers. The ^{1}H nmr spectrum (400 MHz, $CDCl_3$) showed two sets of signals. The following ^{1}H nmr data were attributed to the major isomer: δ 9.72 (m, 1H, -C**H**O), 4.02 (m, 4H, -OC**H**$_2$C**H**$_2$O-), 2.77 (dd, 1H, J = 4.0, J' = 18 Hz, -C**H**HCHO), 2.59 (ddd, 1H, J = 3.0, J' = 10, J'' = 18 Hz, -CH**H**CHO), 1.84 (m, 1H), 1.13 (s, 3H, -C**H**$_3$), 0.85 (s, 3H, -C**H**$_3$) and 0.83 (d, 3H, J = 7 Hz, -CH-C**H**$_3$). The following ^{1}H nmr data were attributed to the minor isomer: δ 9.72 (m, 1H, -C**H**O), 4.02 (m, 4H, -OC**H**$_2$C**H**$_2$O-), 2.48 (ddd, 1H, J = 1.5, J' = 3.5, J'' = 16 Hz, -C**H**HCHO), 2.22 (m, 1H), 0.89 (s, 3H, -C**H**$_3$), 0.86 (s, 3H, -C**H**$_3$) and 0.82 (d, 3H, J = 7 Hz, -CH-C**H**$_3$). The following spectral data were measured for the mixture: ms M$^+$ 226.1566 (calcd. for $C_{13}H_{22}O_3$: 226.1570).

(1S, 4R, 6S)- (101) and (1S, 4R, 6R)-2-oxo-6-(2-oxopropyl)-1,3,3-trimethylbicyclo[2.2.2]octane (102).



101

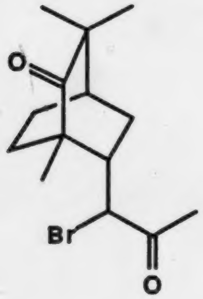


102

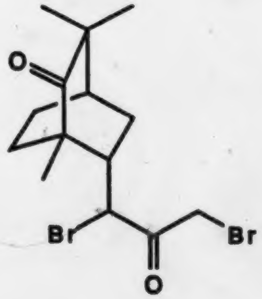
A solution of diethyl 2-oxopropylphosphonate (**99**) (2.73 g, 14.1 mmol, 3.4 eq) in methanol (20 mL) was added to a solution of sodium methoxide (661 mg, 12.2 mmol) in methanol (10 mL). After stirring the mixture for 30 min., a solution of the crude ketal-aldehyde **98** (932 mg, 4.1 mmol) in methanol (5 mL) was added. Stirring was continued at room temperature for 19 hrs. The solvent was evaporated under reduced pressure and the residue was fractionated between methylene chloride and aqueous 5% HCl. The aqueous layer was further extracted with methylene chloride (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford the crude phosphonate adduct (1.19 g). The adduct was dissolved in a mixture of aqueous 3N hydrochloric acid and tetrahydrofuran (1:1, 20 mL) and was then refluxed for 4 hrs. The solution was concentrated under reduced pressure and the residue was extracted with methylene chloride (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The residue was subjected to flash chromatography, (5% ethyl acetate in hexane) to give the bicyclic diketone **101** (344 mg, 34%) as a clear liquid: ^{1}H nmr (400 MHz, $CDCl_3$) δ 2.54 (dd, 1H, *J* = 17, *J'* = 4 Hz, -C**H**HCO-), 2.34 (dddd, 1H, *J* = *11*, *J'* = 10, *J''* = 6, *J'''* = 4 Hz, -C**H**CH$_2$CO-), 2.12 (s, 3H, C**H**$_3$CO-), 2.04 (ddd, 1H, *J* = 14, *J'* = 14, *J'* = 3 Hz, -CH-C**H**H-CH$_2$-), 2.00 (dd, 1H, *J* = 17, *J'* = 11 Hz, -CH**H**CO-), 1.97 (m, 1H), 1.69 (m, 4H), 1.37 (m, 1H, -CH-C**H**H-CH-), 1.13 (s, 3H, -C**H**$_3$), 1.08 (s, 3H, -C**H**$_3$) and 0.86 (s, 3H, -C**H**$_3$); ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 220.6 (p), 206.6 (p), 48.0 (p), 45.3 (p), 45.2 (p), 38.3 (a), 36.8 (a), 31.2 (p), 31.1 (p), 30.1 (a), 24.6 (a), 22.7 (a), 22.0 (p) and 17.9 (a); ir (neat) 1700 cm^{-1} (C=O); ms M$^+$ 222.1620 (calcd. for $C_{14}H_{22}O_2$: 222.1621). Further elution afforded the bicyclic diketone **102**

(302 mg, 30%) as a clear liquid: ^{1}H nmr (400 MHz, CDCl$_3$) δ 2.60 (dd, 1H, $J = 16$, $J' = 4$ Hz, -C**H**HCO-), 2.48 (dd, 1H, $J = 16$, $J' = 11$ Hz, -CH**H**CO-), 2.34 (dddd, 1H, $J = 14$, $J' = 11$, $J' = 3.5$, $J''' = 3$ Hz, -CH-C**H**H-CH-), 2.17 (s, 3H, C**H**$_3$CO-), 2.14 (m, 1H, -C**H**CH$_2$CO-), 1.92 (dddd, 1H,$J = 3.5$, $J' = 7.0$, $J'' = 11$, $J''' = 13$ Hz, -CH-C**H**H-CH$_2$-), 1.78 (ddd, 1H, $J = 14$, $J' = 11.5$, $J' = 4$ Hz, -CH-CH$_2$-C**H**H-), 1.66 (m, 1H, -CH$_2$-C**H**-CH$_2$-), 1.54 (dddd, 1H, $J = 13$, $J' = 11$, $J' = 5$, $J''' = 3$ Hz, -CH-CH**H**-CH-), 1.44 (dddd, 1H, $J = 14$, $J' = 12$, $J' = 5.5$, $J''' = 2$ Hz, -CH-CH$_2$-CH**H**-), 1.16 (s, 3H, -C**H**$_3$), 1.12 (s, 3H, -C**H**$_3$), 1.06 (ddd, 1H, $J = 14$, $J' = 6$, $J' = 2.5$, -CH-CH**H**-CH-) and 0.88 (s, 3H, -C**H**$_3$); ^{13}C nmr (100.6 MHz, CDCl$_3$), δ 221.0 (p), 207.3 (p), 45.8 (p), 44.8 (p), 44.5 (p), 37.9 (a), 32.4 (a), 31.6 (p), 30.2 (a), 25.2 (p), 24.2 (a), 24.1 (a), 22.7 (p) and 17.9 (a); ir (neat) 1710 cm^{-1} (C=O).

Bromination of the bicyclic diketone 102.



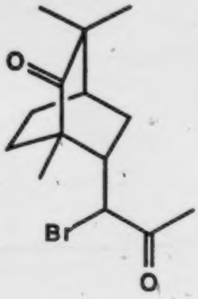
104



105

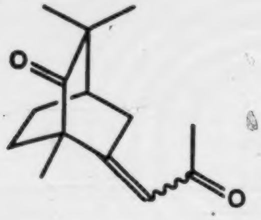
Pyridinium bromide perbromide (189 mg of 80% material, 0.47 mmol, 1.1 eq.) was added at 0°C to a solution of the diketone **102** (95 mg, 0.43 mmol) and acetic acid (0.30 mL) in methylene chloride (1.5 mL). The reaction mixture was stirred at 0°C for 2 hrs. and then poured into water. The resulting suspension was extracted with methylene chloride (4 × 2 mL) and then the combined organic extracts were washed with aqueous 5% sodium bicarbonate (2 × 2 mL), dried (Na_2SO_4) and concentrated. HPMPLC of the residue (2% ethyl acetate in petroleum ether) gave the dibromo diketone **105** (85 mg, 15%): ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.09 (d, 1H, $J = 4$ Hz, -C**H**Br-), 4.39 (d, 1H, $J = 13$ Hz, Br-C**H**H-CO-), 4.06 (d, 1H, $J = 13$ Hz Br-CH**H**-CO-), 2.40-2.15 (m, 3H), 1.92 (m, 1H), 1.80-1.74 (m, 3H), 1.36 (ddd, 1H, $J = 6.0, J' = 12$ Hz), 1.19 (s, 3H, -C**H**$_3$), 1.14 (s, 3H, -C**H**$_3$) and 0.95 (s, 3H, -C**H**$_3$); ms M$^+$ 381.9785, 379.9808 and 377.9827 (calcd. for $C_{14}H_{20}O_2Br$: 381.9790, 379.9810 and 377.9830). Continued elution gave the bromodiketone **104** (85 mg, 66%). ^{1}H nmr (400 MHz, $CDCl_3$) δ 4.63 (d, 1H, $J = 5.0$ Hz, -C**H**Br-), 2.38 (s, 3H, C**H**$_3$-CO-), 2.38-2.19 (m, 3H), 1.92 (m, 1H), 1.78-1.61 (m, 3H), 1.34 (dddd, 1H, $J = 1.5, J' = 6.0, J'' = 12, J''' = 15$ Hz), 1.19 (s, 3H, -C**H**$_3$), 1.14 (s, 3H, -C**H**$_3$) and 0.92 (s, 3H, -C**H**$_3$).

(1S, 4R, 6S, 1'R)- and (1S, 4R, 6S, 1'S)-6-(1-bromo-2-oxopropyl)-2-oxo-1,3,3-trimethylbicyclo[2.2.2]octane (104).



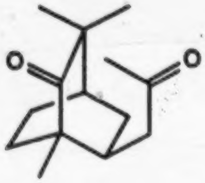
Pyridinium bromide perbromide (208 mg of 80% material, 0.52 mmol, 1.05 eq.) was added to cold (-10°C) solution of the diketone **102** (110 mg, 0.49 mmol) in methylene chloride (1.5 mL) containing acetic acid (0.25 mL). The mixture was stirred at -10°C for 2 hrs. and then poured into water. The resulting suspension was extracted with methylene chloride (3 × 3 mL) and the combined organic extracts were washed with aqueous 5% sodium bicarbonate (2 × 3 mL), dried (Na_2SO_4) and concentrated to give pure bromodiketone **104** (145 mg, 98%). ^{1}H nmr (400 MHz, $CDCl_3$) δ 4.63 (d, 1H, *J* = 5.0 Hz, -C**H**Br-), 2.38 (s, 3H, C**H**$_3$-CO-), 2.38-2.19 (m, 3H), 1.92 (m, 1H), 1.78-1.61 (m, 3H), 1.34 (dddd, 1H, *J* = 1.5, *J'* = 6.0, *J''* = 12, *J'''* = 15 Hz), 1.19 (s, 3H, -C**H**$_3$), 1.14 (s, 3H, -C**H**$_3$) and 0.92 (s, 3H, -C**H**$_3$); ms M$^+$ 302.0703 and 300.0721 (calcd. for $C_{14}H_{21}O_2Br$: 302.0705 and 300.0725).

(1S, 4R)-2-Oxo-6-(2-oxopropenyl)-1,3,3-trimethylbicyclo[2.2.2]-octane (106).



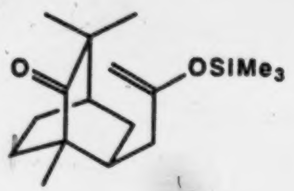
1,4-Diazabicyclo[2.2.2]octane (DABCO) (81 mg, 0.72 mmol, 1.5 eq.) was added to a solution of the bromodiketone **104** (145 mg, 0.48 mmol) in methylene chloride (1.5 mL). The mixture was stirred at room temperature for 13 hrs. Concentration followed by flash chromatography of the residue (5% ethyl acetate in hexane) gave the unsaturated diketone **106** (80 mg, 76% yield) as a slightly yellowish oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.12 (dd, 1H, $J = 2.5$, $J' = 2.5$ Hz, =**CH**), 3.27 (ddd, 1H, $J = 21$, $J' = 6$, $J'' = 3$ Hz), 2.83 (ddd, 1H, $J = 21$, $J' = 3$, $J'' = 3$ Hz), 2.21 (s, 3H, **CH**$_3$-C=O), 1.19 (s, 3H, -**CH**$_3$), 1.14 (s, 3H, -**CH**$_3$) and 1.02 (s, 3H, -**CH**$_3$); ms M$^+$ 220.1460 (calcd. for $C_{14}H_{20}O_2$: 220.1463).

Preparation of compound 101 from the unsaturated diketone 106.



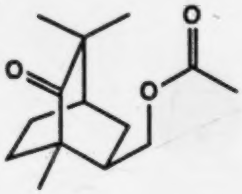
A solution of the unsaturated diketone **106** (43 mg, 0.20 mmol) in ethyl acetate (2 mL) was subjected to hydrogenation at atmospheric pressure using 5% palladium over carbon as catalyst. When the hydrogen takeup ceased, the reaction mixture was filtered and concentrated to give diketone **101** (43 mg, 100%): ^{1}H nmr (400 MHz, $CDCl_3$) δ 2.54 (dd, 1H, J = 17, J' = 4 Hz, -C**H**HCO-), 2.34 (dddd, 1H, J = 11, J' = 10, J' = 6, J''' = 4 Hz, -C**H**CH_2CO-), 2.12 (s, 3H, C**H**$_3$CO-), 2.04 (ddd, 1H, J = 14, J' = 14, J' = 3 Hz, -CH-C**H**H-CH_2-), 2.00 (dd, 1H, J = 17, J' = 11 Hz, -CH**H**CO-), 1.97 (m, 1H), 1.69 (m, 4H), 1.37 (m, 1H, -CH-C**H**H-CH-), 1.13 (s, 3H, -C**H**$_3$), 1.08 (s, 3H, -C**H**$_3$) and 0.86 (s, 3H, -C**H**$_3$); ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 220.6 (p), 206.6 (p), 48.0 (p), 45.3 (p), 45.2 (p), 38.3 (a), 36.8 (a), 31.2 (p), 31.1 (p), 30.1 (a), 24.6 (a), 22.7 (a), 22.0 (p) and 17.9 (a); ir (neat) 1700 cm^{-1} (C=O); ms M^+ 222.1620 (calcd. for $C_{14}H_{22}O_2$: 222.1621).

(1S, 4R, 6S)-2-Oxo-1,3,3-trimethyl-6-(2-trimethylsilyloxy-2-propenyl)-bicyclo[2.2.2]octane (107).



A solution of the bicyclic diketone **101** (19 mg, 0.09 mmol) in tetrahydrofuran (1.5 mL) was added dropwise at -78°C to a solution of lithium diisopropylamide (1.0 mL of 0.106M LDA in THF, 0.11 mmol, 1.2 eq.). After the addition was complete, the reaction mixture was stirred at -78°C for 30 min. and then a 1:1 mixture of chlorotrimethylsilane and triethylamine (60 µL, *ca.* 25 mg of TMSCl, 0.24 mmol, 2.7 eq.) was added at once. The resulting solution was stirred at -78°C for 3 hrs. and then the solvent was concentrated *in vacuo*. The residue was dissolved in hexane and filtered to eliminate the precipitated salts. Concentration of the filtrate followed by bulb to bulb distillation (100-110°C/0.7 torr) gave the trimethylsilyl enol ether **107** (18 mg, 72%) as a yellowish oil: ^{1}H nmr (200 MHz, CDCl$_3$) δ 4.06 (s, 1H, =C**H**), 3.98 (s, 1H, =C**H**), 2.24 (dd, 1H, J = 14, J' = 4 Hz), 1.36 (dd, 1H, J = 14, J' = 13 Hz), 1.12 (s, 3H, -C**H**$_3$), 1.07 (s, 3H, -C**H**$_3$), 0.91 (s, 3H, -C**H**$_3$) and 0.21 (s, 9H, -Si(C**H**$_3$)$_3$).

(1S, 4R, 6R)-6-acetoxymethyl-2-oxo-1,3,3-trimethylbicyclo-[2.2.2]octane (109).



A.- Preparation of peroxytrifluoroacetic acid.

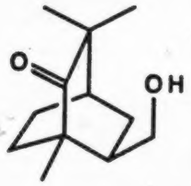
Trifluoroacetic anhydride (0.76 mL, 1.13 g, 5.4 mmol) was added slowly to a cold (0°C) suspension of 90% hydrogen peroxide (0.12 mL, 4.4 mmol) in methylene chloride (4.5 mL). After stirring at 0°C for 15 min. the solution was allowed to warm up to room temperature and used for the oxidation step.

B.- Oxidation.

Peroxytrifluoroacetic acid solution (6.5 mL, 6.34 mmol, 2.9 eq) was added slowly to a stirred mixture of the diketone **101** (495 mg, 2.2 mmol) and disodium hydrogen phosphate (950 mg, 6.7 mmol, 3.0 eq) in methylene chloride (1 mL). The mixture was stirred at room temperature for 2 hrs. and then filtered to eliminate inorganic salts. The precipitate was washed thoroughly with methylene chloride. The combined organic solutions were washed with 5% sodium bicarbonate (5 mL), dried (Na_2SO_4), filtered and concentrated. Bulb to bulb distillation (90-110°C/0.6 torr) afforded the keto-acetate **109** (521 mg, 98%) as a clear oil:

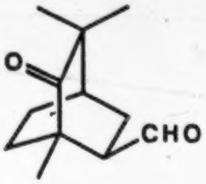
^{1}H nmr (400 MHz, CDCl$_3$) δ 4.04 (dd, 1H, J=11, *J'* = 5 Hz, -**C**H$_2$CO-), 3.84 (dd, 1H, *J* = 11, *J'* = 3 Hz, -**C**H$_2$CO-), 2.04 (m, 1H), 1.97 (m, 1H), 1.96 (s, 3H, **C**H$_3$CO-), 1.89-1.73 (m, 2H), 1.70 (m, 1H, -CH$_2$-**C**H-CH$_2$-), 1.68-1.46 (m, 3H), 1.14 (s, 3H, -**C**H$_3$), 1.13 (s, 3H, -**C**H$_3$) and 0.93 (s, 3H, -**C**H$_3$).

(1S, 4R, 6R)-6-Hydroxymethyl-2-oxo-1,3,3-trimethylbicyclo-[2.2.2]octane (110).



A mixture of keto-acetate **109** (521 mg, 2.2 mmol) and a saturated aqueous solution of potassium carbonate (2 mL) in methanol (3 mL) was stirred at room temperature for 3 hrs. The reaction mixture was then concentrated, dissolved in methylene chloride and filtered. The filtrate was then concentrated to give an oil. Bulb to bulb distillation of the oil (100-120°C/0.6 torr) afforded the hydroxy-ketone **110** (396 mg, 92%) as a clear viscous oil: ^{1}H nmr (400 MHz, CDCl$_3$) δ 3.54 (d, 2H, J = 4.5 Hz, -**C**H$_2$-OH) 2.00-1.55 (m, 8H), 1.15 (s, 3H, -**C**H$_3$), 1.13 (s, 3H, -**C**H$_3$) and 0.97 (s, 3H, -**C**H$_3$); ms M$^+$ 196.1464 (calcd. for $C_{12}H_{20}O_2$: 196.1464).

(1S, 4R, 6R)-6-Carboxaldehyde-2-oxo-1,3,3-trimethylbicyclo-[2.2.2]octane (108).



A.- Preparation of Pyridinium Chlorochromate on Alumina.

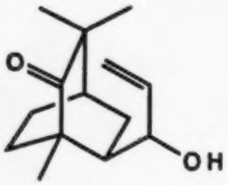
Pyridine (4.85 mL, 4.75 g, 60 mmol, 1.0 eq) was added slowly at 40°C to a solution of chromium trioxide (6.0 g, 60 mmol) in 6N hydrochloric acid (11 mL, 66 mmol, 1.1 eq). The mixture was cooled down to and kept at 10°C until a yellow-orange precipitate formed, and then it was reheated to 40°C to redissolve the solid. Then, neutral active alumina (50 g, Brockmann I, *ca.* 150 mesh) was added to the solution with stirring. After concentration in a rotary evaporator, the solid was dried in a vacuum desiccator overnight at room temperature.

B.- Oxidation.

Pyridinium chlorochromate on alumina (1.57 g, 1.46 mmol of PCC, 2.0 eq) was added to a solution of the hydroxy-ketone **110** (143 mg, 0.73 mmol) in hexane (5 mL). The mixture was stirred at room temperature for 5 hrs. and then filtered through consecutive layers of Silica Gel and neutral Alumina. The solvent was then evaporated *in vacuo* to give the crude keto-aldehyde

108 (122 mg, 86%) as a yellowish oil. This substance proved to be unstable upon standing and therefore the crude material was used immediately for the next reaction.

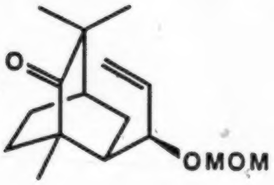
(1S, 4R, 6R, 1'R)- and (1S, 4R, 6R, 1'S)-6-(1-Hydroxy-2-propenyl)-2-oxo-1,3,3-trimethylbicyclo[2.2.2]octane (111).



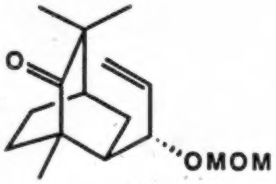
Vinyllithium (0.57 mL of a 1.96 M solution in tetrahydrofuran, 1.12 mmol, 1.5 eq) was added at -78°C to a solution of the keto-aldehyde **108** (145 mg, 0.75 mmol) in tetrahydrofuran (5 mL). The mixture was stirred at -78°C for 10 min. and then methanol (0.5 mL) was added to quench the reaction. The solvent was then evaporated, and the residue was dissolved in methylene chloride, filtered and concentrated. The crude material obtained was filtered through a short column of Silica Gel, eluting with hexane to eliminate grease contained in the vinyllithium solution. Continued elution with 10% ethyl acetate in hexane afforded the unsaturated hydroxy-ketone **111** (144 mg, 87%) as a slightly yellowish oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.80 (ddd, 1H, $J = 17$, $J' = 11$, $J'' = 5$ Hz, CH_2=C**H**-), 5.26 (ddd, 1H, $J = 17$, $J' = J'' = 1.5$ Hz, *cis*- C**H**$_2$=CH-), 5.13 (ddd, 1H, $J = 11$, $J' = J'' = 1.5$ Hz, *trans*-

CH_2=CH-), 4.42 (br. s, 1H, -CH-OH-), 2.00-1.45 (m, 8H), 1.19 (s, 3H, -CH_3), 1.12 (s, 3H, -CH_3) and 1.03 (s, 3H, -CH_3); ms M^+ 222.1619 (calcd. for $C_{14}H_{22}O_2$: 222.1621).

(1S, 4R, 6R, 1'R)- (112) and (1S, 4R, 6R, 1'S)-6-(1-methoxymethoxypropenyl)-2-oxo-1,3,3-trimethylbicyclo[2.2.2]octane (112 and 113).



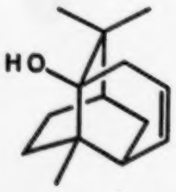
112



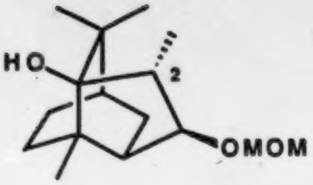
113

A solution of the hydroxy-ketone **111** (225 mg, 1.01 mmol) in dimethoxyethane (0.5 mL) was added to a suspension of sodium hydride (80% material, 70 mg of NaH, 2.3 mmol, 2.3 eq) in dimethoxyethane (0.5 mL). The mixture was stirred at room temperature for 30 min. and then chloromethyl methyl ether (157 µL, 167 mg, 2.07 mmol, 205 eq) was added *via* syringe. After stirring for 2 hrs. the solvent was evaporated *in vacuo*. Water was then added to the residue and the mixture was extracted several times with methylene chloride. The combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (5% ethyl acetate in hexane) gave the MOM-ether **112** (178 mg, 66%) as a yellowish oil: $[\alpha]_D^{22}$ -110° (c = 1.1, $CHCl_3$) and -102° (c = 1.1, CH_3CN); ^1H nmr (400 MHz, $CDCl_3$) δ 5.73 (ddd, 1H, *J* = 7.5, *J'* = 11, *J''* = 17 Hz, C**H**H=CH-), 5.25-4.95 (m, 2H, CH**H**=CH- and CH_2=C**H**-), 4.57 (d, 1H, *J* = 7 Hz, -OC**H**HO-), 4.36 (d, 1H, *J* = 7 Hz, -OCH**H**O-), 4.16 (br. d, 1H, *J* = 8 Hz, -C**H**-O-), 3.36 (s, 3H, -OC**H**$_3$), 2.08 (m, 1H), 2.00-1.83 (m, 2H), 1.70-1.50 (m, 5H), 1.18 (s, 3H, -C**H**$_3$), 1.12 (s, 3H, -C**H**$_3$) and 1.00 (s, 3H, -C**H**$_3$); ir ($CHCl_3$ cast) 1718 cm^{-1} (C=O); ms M^+ 266.1885 (calcd. for $C_{16}H_{26}O_3$: 266.1881). Further elution afforded the MOM-ether **113** (86 mg, 31%): $[\alpha]_D^{22}$ -116° (c = 1.2, $CHCl_3$) and -104° (c = 1.0, CH_3CN); ^1H nmr (400 MHz, $CDCl_3$) δ 5.73 (m, 1H, C**H**H=CH-), 5.26-5.19 (m, 2H, CH**H**=CH- and CH_2=C**H**-), 4.65 (d, 1H, *J* = 7 Hz, -OC**H**HO-), 4.60 (d, 1H, *J* = 7 Hz, -OCH**H**O-), 4.19 (br. d, 1H, *J* = 8 Hz, -C**H**-O-), 3.35 (s, 3H, -OC**H**$_3$), 2.04 (m, 1H), 1.99-1.82 (m, 2H), 1.78-1.51 (m, 5H), 1.16 (s, 3H, -C**H**$_3$), 1.10 (s, 3H, -C**H**$_3$) and 0.90 (s, 3H, -C**H**$_3$); ir ($CHCl_3$ cast) 1715 cm^{-1} (C=O); ms M^+ 266.1881 (calcd. for $C_{16}H_{26}O_3$: 266.1881).

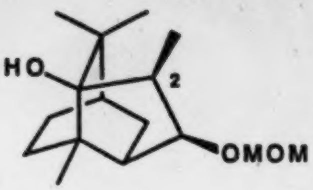
(+)-Norpatchoulenol (15).



15



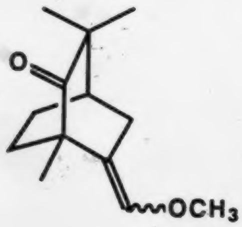
117



118

Metallic sodium (62 mg, 2.70 mmol, 15 eq) was added to a solution of the MOM ether **112** (48 mg, 0.18 mmol) in dimethoxyethane (3 mL). The mixture was heated at reflux temperature for 3 hrs. and then allowed to cool to room temperature. Methanol (1 mL) was added slowly to destroy the excess of sodium and then water (2 mL) was added. The resulting mixture was extracted with ethyl ether (5 × 2 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Flash chromatography of the residue (5% ethyl acetate in hexane) gave norpatchoulenol (**15**) (5.2 mg, 14%): $[\alpha]_D^{22}$ +19° (c = 0.35, CH_3CN); ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.71 (ddd, 1H, $J = 3.0$, $J' = 6.0$, $J'' = 10$ Hz, -C**H**=CH-), 5.49 (ddd, 1H, $J = 2.0$, $J' = 5.0$, $J'' = 10$ Hz, -CH=C**H**-), 2.38 (dd, 1H, $J = 4.5$, $J' = 18$ Hz), 1.85-1.55 (m, 3H), 1.50-1.30 (m, 3H), 1.10 (s, 6H, -C**H**$_3$) and 0.81 (s, 3H, -C**H**$_3$); ir ($CHCl_3$ cast) 3620 (free OH), 3500 (bonded OH) and 1650 cm^{-1} (C=C); ms M$^+$ 206.1675 (calcd. for $C_{14}H_{22}O$: 206.1671). Continued elution afforded compound **117** (22 mg, 46%): ^{1}H nmr (400 MHz, $CDCl_3$) δ 4.70 (d, 1H, $J = 7.0$ Hz -OC**H**HO-), 4.57 (d, 1H, $J = 7.0$ Hz, -OCH**H**O-), 3.58 (br. d, 1H, J = 8.0 Hz, -C**H**-O-), 3.34 (s, 3H, -OC**H**$_3$), 2.79 (br. quintet, 1H, J = 8.0 Hz, -C**H**-CH$_3$), 1.84 (m, 2H), 1.73-1.57 (m, 2H), 1.37-1.10 (m, 4H), 1.08 (s, 3H, -C**H**$_3$),, 1.01 (d, 3H, J = 8.0 Hz, -CH-C**H**$_3$), 0.95 (s, 3H, -C**H**$_3$) and 0.92 (s, 3H, -C**H**$_3$); ir (CHCl$_3$ cast) 3520, 1460, 1450 cm^{-1}; ms M$^+$ 268.2038 (calcd. for $C_{16}H_{28}O_3$: 268.2038). Further elution gave the hydroxy-ether **118** (12 mg, 27%): ^{1}H nmr (400 MHz, CDCl$_3$) δ 4.71 (d, 1H, J = 7.0 Hz, -OC**H**HO-), 4.62 (d, 1H, J = 7.0 Hz, -OCH**H**O-), 3.39 (d, 1H, J = 6.5 Hz, -C**H**-O-), 3.37 (s, 3H, -OC**H**$_3$), 2.44 (br. quintet, 1H, J = 7.5 Hz, -C**H**-CH$_3$), 1.90-1.80 (m. 2H), 1.87-1.52 (m, 4H), 1.36 (ddd, 1H, J = 3.0, J' = 12, J'' = 14 Hz), 1.24 (d, 3H, J = 7.5 Hz, -CH-C**H**$_3$), 1.06 (s, 3H, -C**H**$_3$), 1.05 (s, 3H, -C**H**$_3$) and 0.99 (s, 3H, -C**H**$_3$); ir (CHCl$_3$ cast) 3580, 1470 and 1460 cm^{-1}; ms M$^+$ 260.2040 (calcd. for $C_{16}H_{28}O_3$: 268.2038).

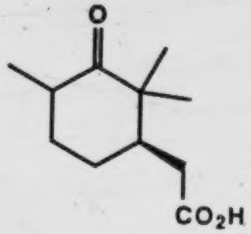
Cis- and _trans_-(1S, 4R)-6-(methoxymethylene)-2-oxo-1,3,3-trimethylbicyclo[2.2.2]octane (123).



Potassium hydride (262 mg of 35% material, 92 mg, 2.88 mmol, 5.8 eq) was added with stirring to a mixture of dimethyl sulfoxide

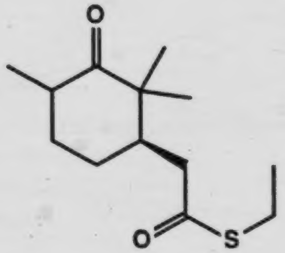
(1 mL) and benzene (1 mL) at room temperature. The stirring was continued until the evolution of hydrogen ceased and the solution became clear. Then, methoxymethyltriphenylphosphonium chloride (353 mg of 90% material, 318 mg, 0.93 mmol, 2.4 eq) was added and the mixture was stirred for two hours, after which a solution of the keto-ester **89** (83 mg, 0.39 mmol) in benzene (1 mL) was added. The reaction was stirred for further two hours and then water (1 mL) was added. The resulting solution was extracted with ethyl ether (5 × 2 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The residue was subjected to flash chromatography (5% ethyl ether in hexane) to give the enol-ether **123** (42 mg, 52%) as a 7:1 mixture of isomers: ^1H nmr (400 MHz, $CDCl_3$) δ 5.87 and 5.82 (each t, total 1H, $J_1 = 2.0$, $J_2 = 3.0$ Hz, =C**H**), 2.65 (dq, 1H, $J = 3.0$, $J' = 18$ Hz, -CH_2-C**H**H-CH-), 2.22 (dt, 1H, $J = 3.0$, $J' = 18$ Hz, -CH_2-CH**H**-CH-), 1.82 (quintet, 1H, $J = 3.0$ Hz), 1.15 (s, 3H, -C**H**$_3$), 1.07 (s, 3H, -C**H**$_3$) and 1.03 (s, 3H, -C**H**$_3$); ir ($CHCl_3$ cast) 1717 (C=O) and 1671 cm^{-1} (C=C); ms M^+ 208.1469 (calcd. for $C_{13}H_{20}O_2$: 208.1458).

(3R, 6R)- and (3R, 6S)-3-carboxymethyl-2,2,6-trimethylcyclohexanone (127).



A mixture of the keto-ester **89** (900 mg, 4.24 mmol), lithium iodide (2.84 g, 21.2 mmol, 5.0 eq) and water (0.20 mL, 200 mg, 11 mmol, 2.6 eq) in pyridine (10 mL) was heated at reflux temperature for 16 hours and then allowed to cool to room temperature. The reaction mixture was diluted with a 2:1 mixture of ethyl ether and methylene chloride (50 mL) and the resulting solution was washed with 5% aqueous hydrochloric acid (3 × 15 mL) and then extracted with 15% aqueous sodium hydroxide (3 × 15 mL). The alkaline extracts were acidified to pH 1 with ice-cold, concentrated hydrochloric acid and the resulting suspension was extracted with methylene chloride (5 × 10 mL), dried (Na_2SO_4), filtered and concentrated. Bulb to bulb distillation of the residue (110-120°C/0.6 torr) gave keto-acid **127** (740 mg, 88%) as a 2:1 mixture of epimers. The following ^{1}H nmr data (400 MHz, $CDCl_3$) were attributed to the major isomer: δ 2.66 (ddd, 1H, J = 6.0, J' = 12, J'' = 19 Hz), 2.54 (dd, 1H, J = 3.0, J' = 16 Hz), 2.22 (dd, 1H, J = 10, J' = 15 Hz), 1.30 (s, 3H, -CH_3), 1.11 (s, 3H, -CH_3), 1.05 (s, 3H, -CH_3) and 1.00 (d, 3H, $J = 6.0$ Hz, -CH-CH_3). The following spectral data were recorded on the mixture: ir ($CHCl_3$ cast) 3500-2600 (COOH), 1737 (carboxyl C=O) and 1706 cm^{-1} (ketone C=O); ms M^+ 198.1253 (calcd. for $C_{11}H_{18}O_3$: 198.1256). Anal. calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; found: C,66.50; H, 9.02.

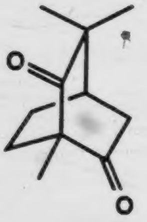
(3R, 6R)- and (3R, 6S)-3-(2-oxo-3-thiapentyl)-2,2,6,trimethylcyclohexanone (126).



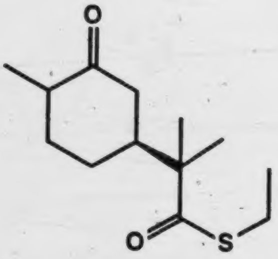
A mixture of the keto-acid **127** (740 mg, 3.7 mmol), pyridine (0.90 mL, 0.88 g, 11.2 mmol, 3.0 eq), ethanethiol (0.55 mL, 465 mg, 7.5 mmol, 2.0 eq) and phenyl dichlorophosphate (0.84 mL, 1.18 g, 5.6 mmol, 1.5 eq) in methylene chloride (10 mL) was stirred at room temperature for 24 hours. The reaction mixture was then diluted with ethyl ether (20 mL), extracted with 1N aqueous sodium hydroxide (2 × 5 mL), dried (Na_2SO_4), filtered and concentrated. Bulb to bulb distillation of the residue (90-100°C/0.6 torr) gave compound **126** (895 mg, 99%) as a 2:1 mixture of epimers: ^1H nmr (400 MHz, $CDCl_3$)

δ 2.68 (q, 2H, $-\mathbf{CH}_2CH_3$), 2.44 and 2.30 (dd, both 1H, J = 11, J' = 15 Hz), 1.25 and 1.24 (t, both 3H, J = 7.0 Hz, $-CH-\mathbf{CH}_3$), 1.10 (s, 3H, $-\mathbf{CH}_3$), 1.04 (s, 3H, $-\mathbf{CH}_3$), 1.00 and 0.99)each d, total 3H, J = 6.5 Hz, $-CH-\mathbf{CH}_3$); ir ($CHCl_3$ cast) 1705 (ketone C=O) and 1689 cm^{-1} (thiol ester C=O); ms M^+ 242.1343 (calcd. for $C_{13}H_{22}O_2S$: 242.1340).

(1S, 4R)-2,6-dioxo-1,3,3-trimethylbicyclo[2.2.2]octane (122) and (3R, 6R)- and (3R, 6S)-3-(1,1-dimethyl-2-oxo-3-thiapentyl)-6-methylcyclohexanone (128).



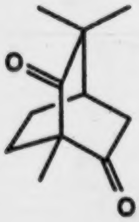
122



128

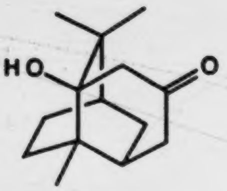
A solution of the thiol ester **126** (119 mg, 0.50 mmol) in tetrahydrofuran (1 mL) was added at -78°C to a solution of lithium diisopropylamide (0.53 mmol, 1.05 eq) in tetrahydrofuran. The mixture was stirred at -78°C for 4 hrs. and then the reaction was quenched by addition of water (1 mL). The resulting suspension was extracted with ether (5 × 3 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Flash chromatography (3% ethyl acetate in hexane) of the residue afforded a 1:1 mixture of epimers of a compound that has been tentatively identified as **128** (26 mg, 22%): ^{1}H nmr (400 MHz, CDCl$_3$) δ 2.88 (q, 2H, *J* = 7.5 Hz, -C**H**$_2$CH$_3$), 2.63 (m, 1H, -C**H**-CH$_3$), 2.23 (m, 2H) 1.74 (m, 2H), 1.56 (m, 2H), 1.26 and 1.25 (each t, both 3H, *J* = 7.5 Hz, -CH$_2$C**H**$_3$), 0.99 (s, 3H, -C**H**$_3$), 0.88 and 0.87 (each d, both 3H, *J* = 6.5 Hz, -CH-C**H**$_3$) and 0.80 (s, 3H, -C**H**$_3$); ir (CHCl$_3$ cast) 1736 and 1691 cm^{-1}. Continued elution gave the diketone **122** (13 mg, 15%): ^{1}H nmr (400 MHz, CDCl$_3$) δ 2.71 (dt, 1H, *J* = 3.0, *J'* = 19 Hz, -C**H**H-CO-), 2.41 (dd, 1H, *J* = 3.0, *J'* = 19 Hz, -CH**H**-CO-), 2.19 (m, 1H, -C**H**H-CH-), 2.14 (quintet, 1H, -C**H**-), 1.88 (m, 2H, -C**H**$_2$-C-CH$_3$), 1.80 (m, 1H, -CH**H**-CH-), 1.29 (s, 3H, -C**H**$_3$), 1.09 (s, 3H, -C**H**$_3$) and 1.08 (s, 3H, -C**H**$_3$); ^{13}C nmr (100.6 MHz, CDCl$_3$) δ 213.0, 208.4, 62.3, 45.9, 41.9, 38.3, 29.7, 24.3, 23.8, 22.2 and 12.4; ir (CHCl$_3$ cast) 1736 and 1707 cm^{-1} ; ms M$^+$ 180.1147 (calcd. for $C_{11}H_{16}O_2$: 180.1150). Further elution afforded a complex mixture of substances (13 mg).

(1S, 4R)-2,6-dioxo-1,3,3-trimethylbicyclo[2.2.2]octane (122).



A mixture of the keto-acid **127** (260 mg, 1.3 mmol), polyphosphoric acid (1.0 g) and acetic acid (2 mL) was heated at 100°C for 4 hrs. After allowing the reaction mixture to cool to room temperature, water (5 mL) was added and the resulting solution was extracted with ether (5 × 5 mL). The combined organic extracts were washed with 5% aqueous sodium bicarbonate (2 × 5 mL), dried (Na_2SO_4), filtered and concentrated. Dry column flash chromatography of the residue gave the diketone **122** (60 mg, 25%): ^{1}H nmr (400 MHz, $CDCl_3$) δ 2.71 (dt, 1H, J = 3.0, J' = 19 Hz, -C**H**H-CO-), 2.41 (dd, 1H, J = 3.0, J' = 19 Hz, -CH**H**-CO-), 2.19 (m, 1H, -C**H**H-CH-), 2.14 (quintet, 1H, -C**H**-), 1.88 (m, 2H, -C**H**$_2$-C-CH_3), 1.80 (m, 1H, -CH**H**-CH-), 1.29 (s, 3H, -C**H**$_3$), 1.09 (s, 3H, -C**H**$_3$) and 1.08 (s, 3H, -C**H**$_3$); ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 213.0, 208.4, 62.3, 45.9, 41.9, 38.3, 29.7, 24.3, 23.8, 22.2 and 12.4; ir ($CHCl_3$ cast) 1736 and 1707 cm^{-1} ; ms M$^+$ 180.1150 (calcd. for $C_{11}H_{16}O_2$: 180.1150). Continued elution gave an unidentified material (60 mg): ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.70 (t, 1H, J = 2.0 Hz), 4.44 (d, 1H, J = 2.0 Hz), 2.76 (ddd, 1H, J = 2.0, J' = 5.0, J'' = 14 Hz), 2.33 (dddd, 1H, J = 2.0, J' = 7.0, J'' = 14, J''' = 15 Hz), 1.71 (dddd, 1H, J = 2.0, J' = 3.5, J'' = 7.0, J''' = 13 Hz), 1.57 (dddd, 1H, J = 3.0, J' = J'' = 7.0, J''' = 19 Hz), 1.37 (ddd, 1H, J = 5.0, J' = 13, J'' = 26 Hz), 1.18 (s, 3H, -C**H**$_3$), 0.92 (d, 1H, J = 7.0 Hz) and 0.57 (s, 3H, -C**H**$_3$); ir ($CHCl_3$ cast) 1810, 1735 and 1644 cm^{-1}; ms M$^+$ 180.1150.

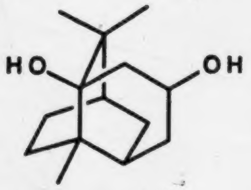
(1R, 5S, 7R, 10S)-1-Hydroxy-3-oxo-10,11,11-trimethyltricyclo-[5.3.1.$0^{5,10}$]undecane (76).



n-Butyllithium (2.0 mL of a 2.5 M solution in hexane, 7.0 mmol, 7.0 eq) was added at -78°C to a solution of diisopropylamine (1.0 mL, 0.74 g, 7.3 mmol, 7.3 eq) in tetrahydrofuran (4 mL). After stirring at -78°C for 15 min. the mixture was allowed to warm up to room temperature and then a solution of the diketone **101** (221 mg, 0.99 mmol) in tetrahydrofuran (1 mL) was added *via* syringe. The stirring was continued at room temperature for 5 days, after which water (1 mL) was added. The resulting suspension was extracted with methylene chloride (5 × 5 mL) and then the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. HPMPLC of the residue (10% ethyl acetate in hexane) gave starting material (108 mg, 49% recovery). Continued elution gave the hydroxy-ketone **76** (67 mg, 59% based on the consumed starting material): ^{1}H nmr (400 MHz, $CDCl_3$) δ 2.74 (dd, 1H, J = 2.0, J' = 16 Hz, -C(OH)C**H**HCO-), 2.57 (dd, 1H, J = 5.0, J' = 16 Hz, -CHC**H**HCO-), 2.30 (d, 1H, J = 16 Hz, -C(OH)CH**H**CO-), 2.18 (m, 1H), 1.94 (m, 3H), 1.72 (m, 2H), 1.11 (s, 3H, -C**H**$_3$), 1.03 (s, 3H, -C**H**$_3$) and

0.95 (s, 3H, -**CH**$_3$); ^{13}C nmr (100.6 MHz, CDCl$_3$) δ 211.4, 77.8, 50.5, 45.3, 40.6, 38.1, 37.1, 36.6, 30.8, 27.5, 25.7, 25.5, 23.7 and 20.5; ir (CHCl$_3$ cast) 3514 (OH) and 1702 cm^{-1} (C=O); ms M$^+$ 222.1619 (calcd. for $C_{14}H_{22}O$: 222.1619). Anal. calcd. for $C_{14}H_{22}O$: C, 75.63; H, 9.97; found: C, 75.68; H, 10.05.

(1R, 3R, 5S, 7R, 10S)-1,3-Dihydroxy-10,11,11-trimethyltricyclo-[5.3.1.0^{5,10}]undecane (132).



A mixture of the hydroxy-ketone **76** (26 mg, 0.12 mmol), and sodium borohydride (21 mg, 0.59 mmol, 4.8 eq) in ethanol (0.5 mL) was stirred at room temperature for 6 hrs. Then, saturated aqueous ammonium chloride solution (1 mL) was added and the resulting solution was extracted with methylene chloride (5 × 2 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated to give the pure diol **132** (26 mg, 100%): ^{1}H nmr (400 MHz, CDCl$_3$) δ 4.30 (t, 1H, J = 7.0 Hz, -**CH**OH), 2.30 (dddd, 1H, J =J' = 3.0, J'' = 6.0, J''' = 13 Hz), 2.13 (dd, 1H, J = 2.0, J' = 16 Hz), 2.03 (ddd, 1H, J = 4.0, J' = 6.5, J'' = 15 Hz), 1.89 (m, 2H), 1.82 (dd, 1H, J = 7.0, J' = 16 Hz), 1.67 (m, 1H), 1.51 (m, 2H), 1.26 (s, 3H, -**CH**$_3$), 1.12 (s, 3H, -**CH**$_3$) and

0.79 (s, 3H, -CH$_3$); ^{13}C nmr (100.6 MHz, CDCl$_3$) δ 76.5(p), 67.1 (a), 39.7 (a), 36.7 (a), 36.2 (p), 33.9 (p), 29.1 (p), 28.6 (p), 26.9 (a), 24.2 (p) and 20.5 (a); ir (CHCl$_3$ cast) 3513 and 3466 cm^{-1} (OH); ms M$^+$ 224.1762 (calcd. for $C_{14}H_{24}O_2$: 224.1763).

Chapter 2

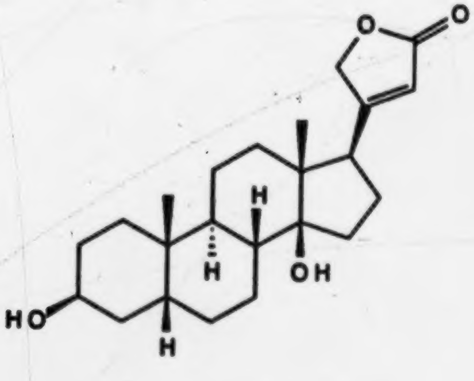
Studies Towards the Synthesis of Strophanthidin

Introduction

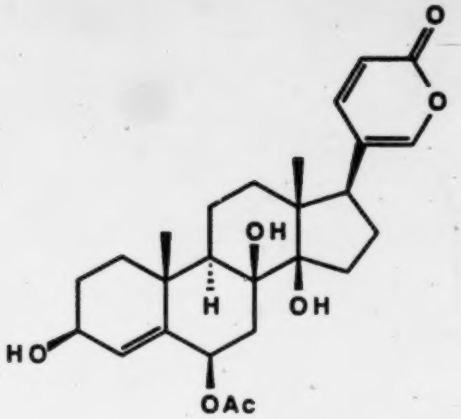
Steroidal compounds having the ability to exert a specific action on the cardiac muscle on injection into humans or animals are described as cardiac-active or cardiotonic principles.[82] The more typical members of this group of physiologically active chemical substances are glycosides of plant origin; hydrolysis splits off the glycosidic portion and gives a steroid aglycone, or genin. Cardiac glycosides occur in small amounts in plants of wide geographical distribution, particularly those of the order *Apocynaceae*.[83] Many species grow in tropical regions and have been employed by natives of Africa and South America for the preparation of arrow poisons.

Digitalis, a preparation made by extraction of dried seeds and leaves of the purple foxglove, *Digitalis purpurea*, was introduced in heart therapy in 1785 by the Scottish physician William Withering and was met with great success. Chemical investigations of the active principles of the digitalis plants date from the early nineteenth century. In 1938, Cattell and Gold[84] demonstrated that digitalis increases the force of contraction in the isolated cat papillary muscle. The subcellular basis of the inotropic effect of these substances is a reduction in the Na^+, K^+-ATPase activity.[85,86] Binding of the drug to the enzyme at the outer surface of the cell membrane brings about a change in the conformation of the protein in such a way that it looses its ability to bind ATP and therefore its activity. The net result is a decrease in the activity of the sodium pump and therefore an increase in the force of contraction, improving cardiac efficiency and lowering the heart rate. Some cardiotonic steroids have been shown to possess strong cytotoxic activity against human carcinoma of the nasopharynx carried in cell culture (KB).[87-89]

Chemically, the aglycones of the cardiotonic steroids are divided in two types: cardenolides and bufadienolides. The more prevalent cardenolides, exemplified by digitoxigenin (**133**), are C_{23} steroids bearing a 17β-oriented α,β-butenolide ring and generally a 14β-hydroxyl group.[90] Additional substitution by ketone, hydroxyl, aldehyde, epoxide and olefin groups gives rise to various genin portions. The bufadienolides, on the other hand, bear a 5-substituted 2-pyrone ring in the 17β-position; otherwise the steroid ring substituents and stereochemistry resemble those of the cardenolides [e.g.: scillirosidin, (**134**)].

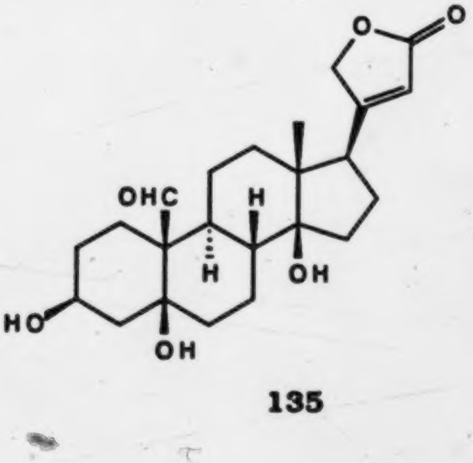


133



134

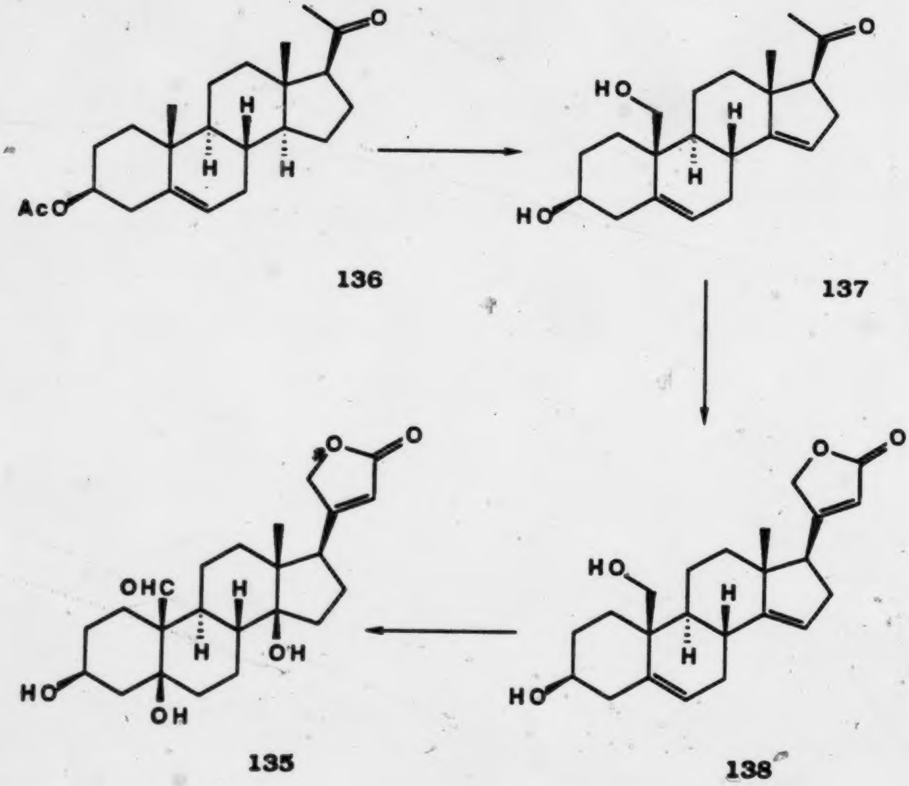
Much of the pioneering work[91] (1922-1934), carried out by W. A. Jacobs of the Rockefeller Institute towards the structural problem of cardiotonic steroids, was done on strophanthidin (**135**). This substance is obtained from glycosides present in the seeds of *Strophanthus kombé* and turned out to be one of the more elaborate aglycones since it has an aldehydic function at C-19.



135

To this date, only two synthetic studies have been reported for strophanthidin (**135**). In 1978, Yoshii and coworkers published their partial synthesis of **135**.[92] These authors employed the readily available pregnenolone acetate (**136**) as the starting material and elaborated it into strophanthidin in three main stages (Scheme 17).

Scheme 17

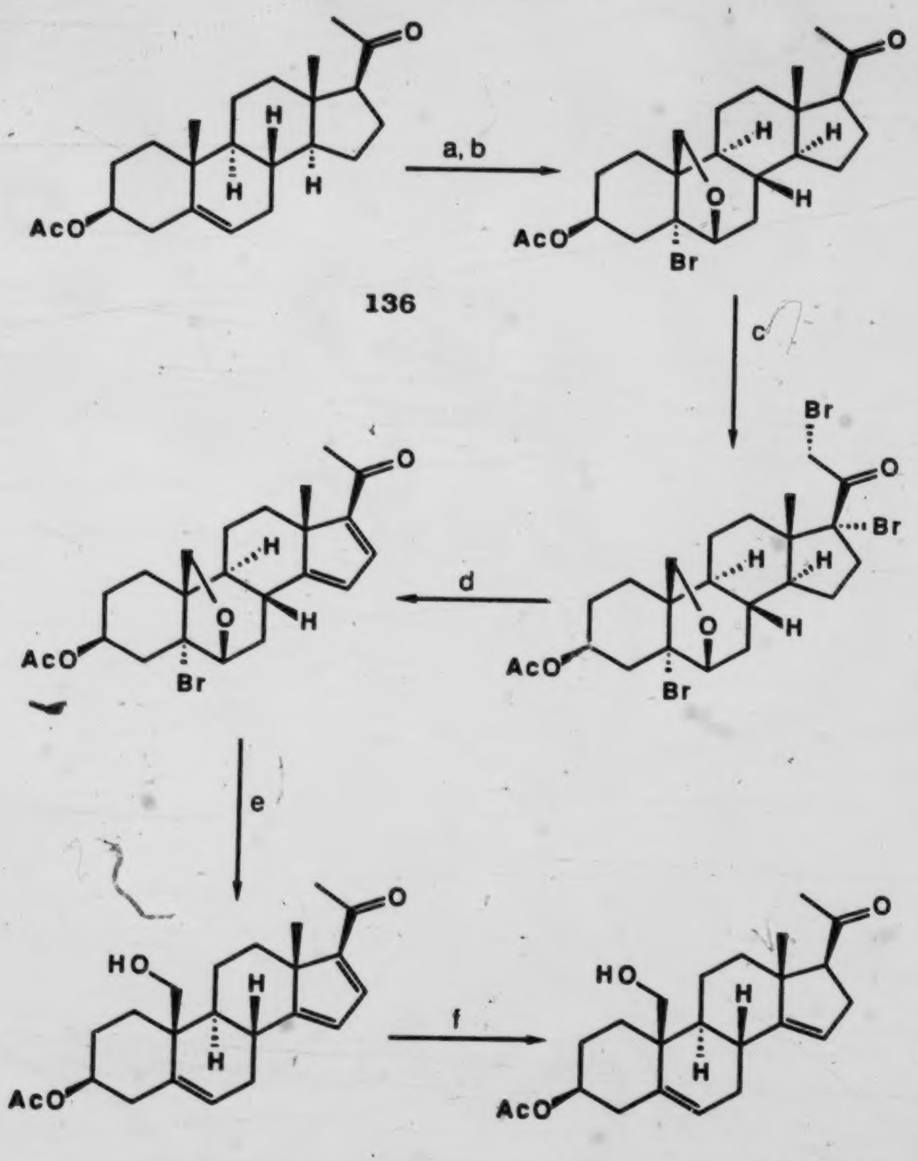

AcO
H
H
H
O
136
HO
HO
H
H
O
137
O
O
HO
HO
H
H
138
O
O
OHC
HO
H
H
OH
OH
135

The first phase involved the conversion of the unactivated C-19 methyl group into a hydroxymethyl substituent, and the introduction of the C-14 double bond to give the dihydroxydienone **137**. This transformation was achieved as shown in Scheme 18.

The next task consisted of the construction of the butenolide ring without affecting the functional groups in the steroid skeleton. It was performed by a reaction sequence (Scheme 19) involving the initial conversion of compound **139** into the 21-methylthio derivative **140** by means of a base-catalyzed reaction with diethyl oxalate followed by treatment of the resulting compound with methyl thiotosylate in the presence of potassium acetate in ethanol. Reformatsky reaction of the corresponding diacetate gave compound **141**, which was treated with trimethyloxonium tetrafluoroborate followed by sodium hydroxide, to give the epoxy-ester **142**. The latter substance was adsorbed on alumina for 1 to 5 hours to afford the diacetate **143**.

The third stage of the synthesis involved the formation of the two tertiary β-hydroxy groups at the 5 and 14 positions, followed by the selective oxidation of the 19-hydroxymethyl moiety (Scheme 20).

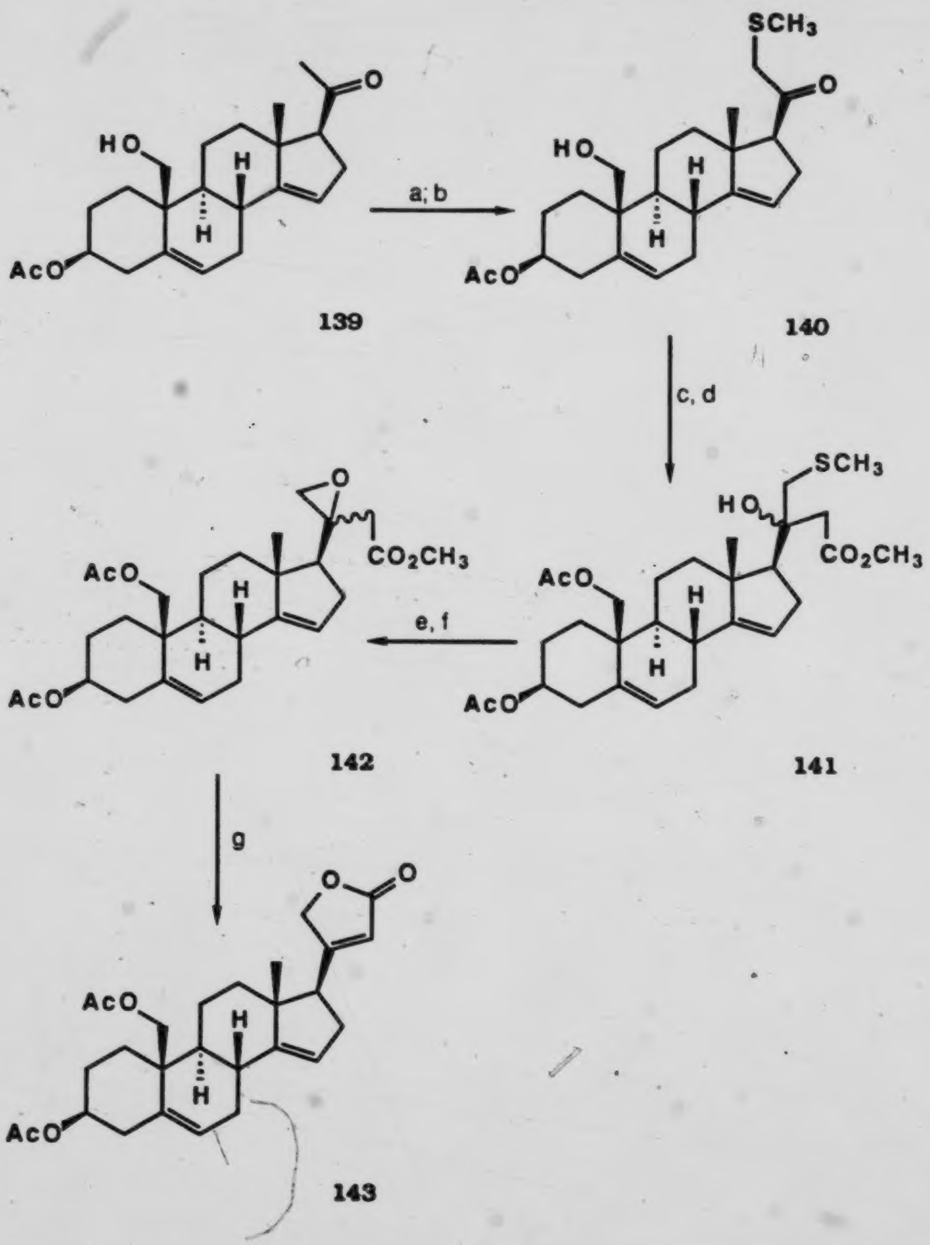
Scheme 18



O
H
H
H
AcO
a, b
O
H
H
O
H
AcO
Br
136
c
Br
O
Br
H
H
O
H
AcO
Br
d
O
H
O
H
AcO
Br
e
O
HO
H
H
AcO
f
O
HO
H
H
AcO
139

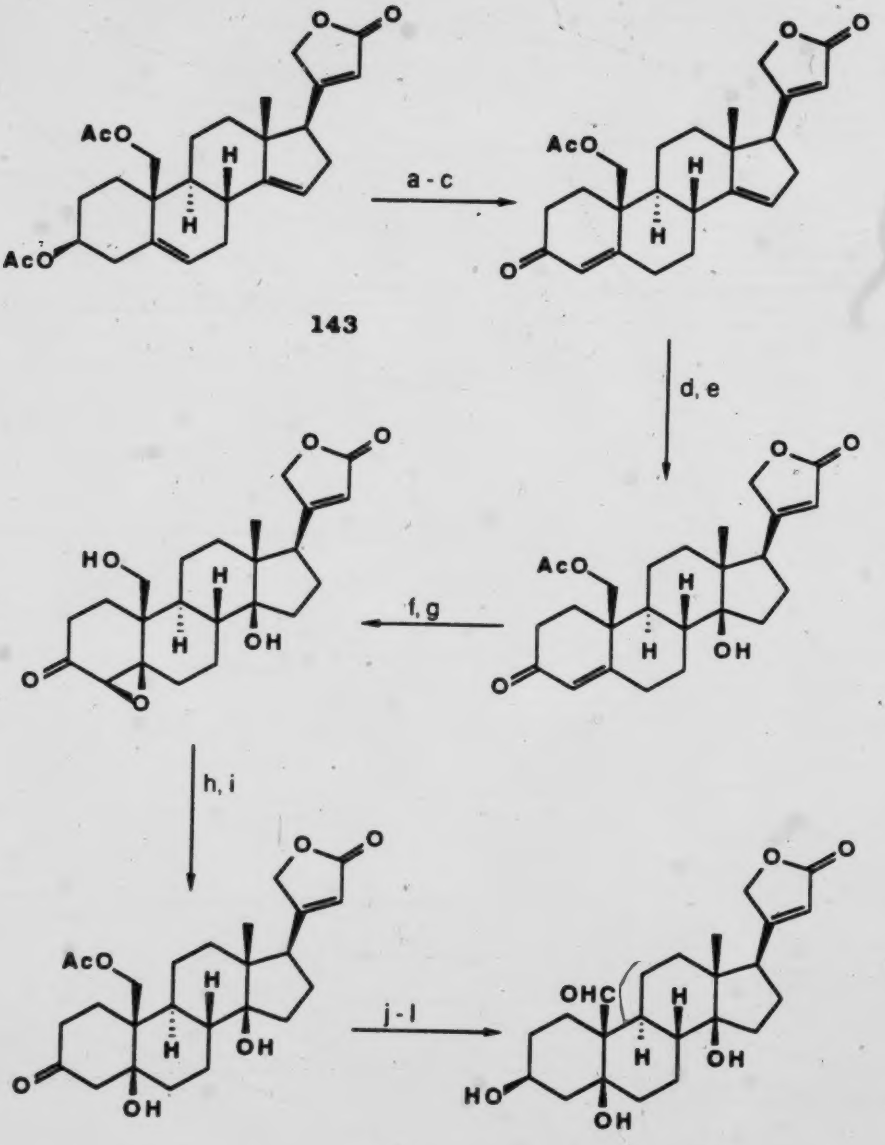
(a) HOBr; (b) Pb(OAc)$_4$; (c) Br$_2$, AcOH; (d) LiBr, DMF; (e) Zn, i-PrOH, AcOH; (f) Ph$_3$SnH, toluene.

Scheme 19


SCH3
HO
AcO
H
a; b
c, d
e, f
g
CO2CH3
139
140
141
142
143

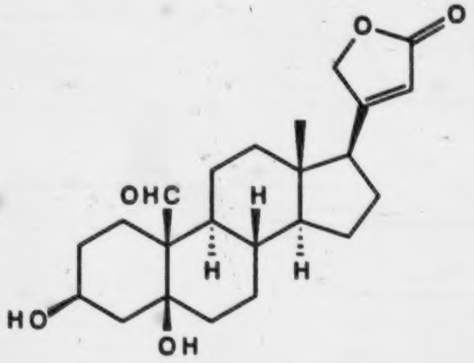
(a) (CO$_2$Et)$_2$, KOMe; (b) TsSMe, KOAc; (c) Ac$_2$O, pyridine; (d) BrCH$_2$CO$_2$Me, Zn; (e) Me$_3$O$^+$BF$_4^-$; (f) 0.5 N NaOH, CH$_2$Cl$_2$; (g) alumina.

Scheme 20


AcO
AcO
H
H
143
a - c
AcO
O
H
H
d, e
AcO
O
H
H
OH
f, g
HO
O
H
H
OH
O
h, i
AcO
O
H
H
OH
OH
j - l
OHC
HO
H
H
OH
OH
135

(a) 2M $KHCO_3$, MeOH; (b) PCC, CH_2Cl_2; (c) $(CO_2H)_2$; (d) AcNHBr, H_2O; (e) Raney nickel; (f) 2M $KHCO_3$, MeOH; (g) H_2O_2, NaOH; (h) Ac_2O, pyridine; (i) $Cr(OAc)_2$; (j) Urushibara nickel A; (k) 2M $KHCO_3$, MeOH; (l) CrO_3, $(Me_2N)_3PO$.

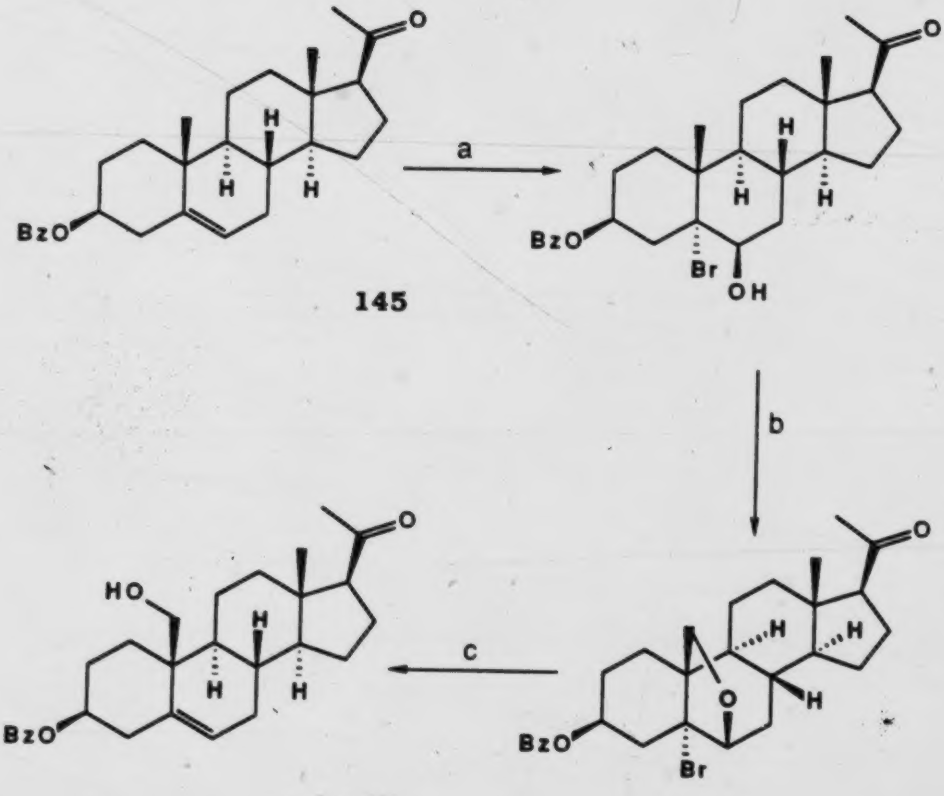
The second series of studies directed towards the preparation of strophanthidin have been carried out by Kocovsky *et al.*[93-96] and culminated in the isolation of 14-deoxy-14α–strophanthidin (**144**).



144

The starting material used was pregnenolone benzoate (**145**). The oxidation of C-19 was implemented by means of the same methodology employed by Yoshii, to produce compound **146** (Scheme 21). The butenolide moiety was formed using an intramolecular Wittig reaction, as shown in Scheme 22. The hydroxyl functionality at C-19 was then recovered by means of a two-step procedure, involving the treatment of **147** with hypobromous acid followed by reduction with zinc in hot acetic acid, to afford the alcohol **148** (Scheme 23). Formylation of **148** followed by treatment with hypobromous acid gave the bromohydrin **149**, which was dehalogenated with Raney nickel. Finally, oxidation of the C-19 hydroxyl group and saponification of the benzoate produced compound **144**.

Scheme 21



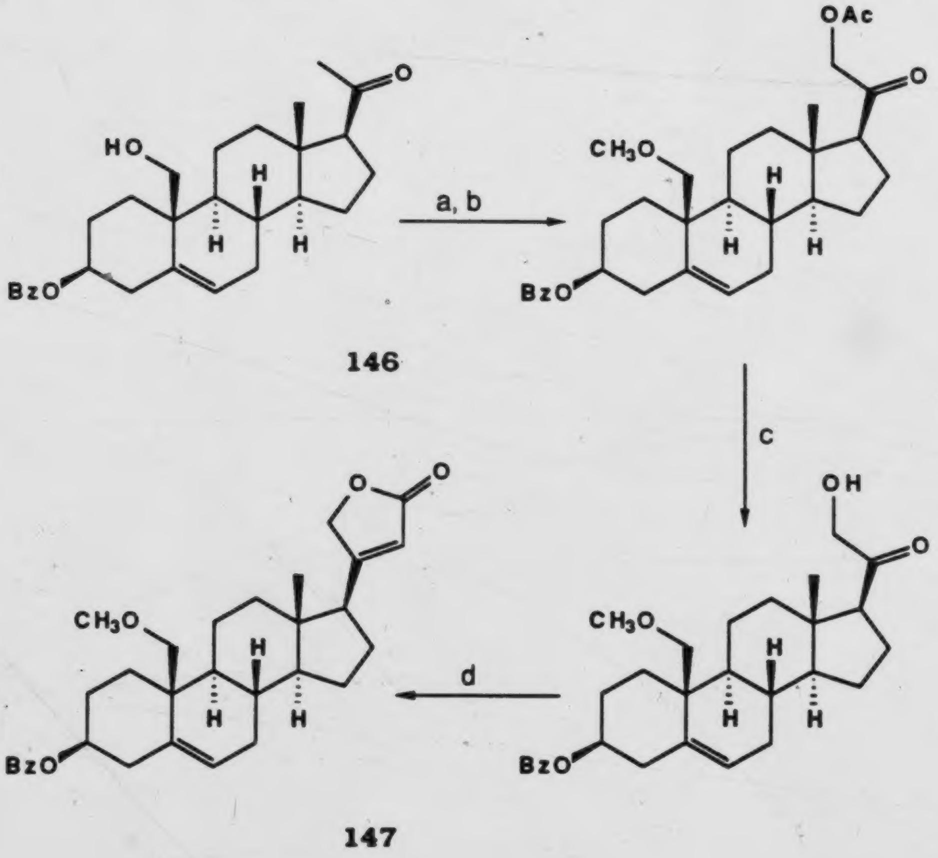
a
b
c
BzO
Br
OH
HO
O
H

145

146

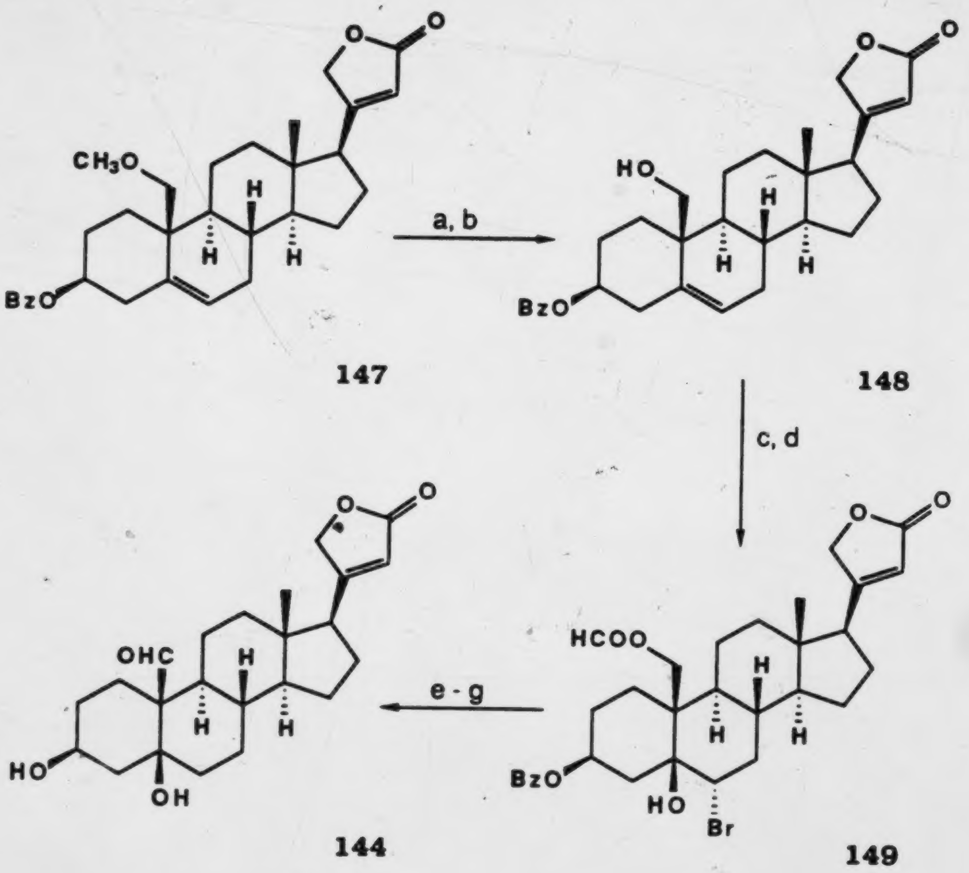
(a) NBA, $HClO_4$, dioxane; (b) $Pb(OAc)_4$, I_2, benzene; (c) Zn, AcOH.

Scheme 22


OAc
HO
CH₃O
H
BzO
a, b
146
c
OH
d
147

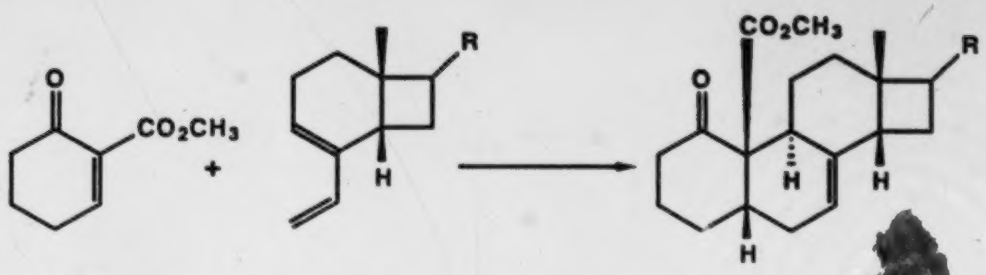
(a) 1)NaH, DME; 2)CH_3I; (b) $Pb(OAc)_4$, $BF_3{\cdot}OEt_2$, MeOH, benzene; (c) $HClO_4$, MeOH, $CHCl_3$; (d) 1)DCC, $(EtO)_2POCH_2CO_2H$, benzene; 2)t-BuOK, DME.

Scheme 23


CH₃O
BzO
H
a, b
HO
BzO
c, d
OHC
HO
OH
e - g
HCOO
BzO
HO
Br
147
148
144
149

(a) NBA; $HClO_4$, dioxane; (b) Zn, AcOH; (c) HCO_2H, 70°C; (d) NBA, $HClO_4$, dioxane; (e) Raney nickel, EtOH; (f) CrO_3, acetone; (g) $KHCO_3$, MeOH, H_2O, reflux.

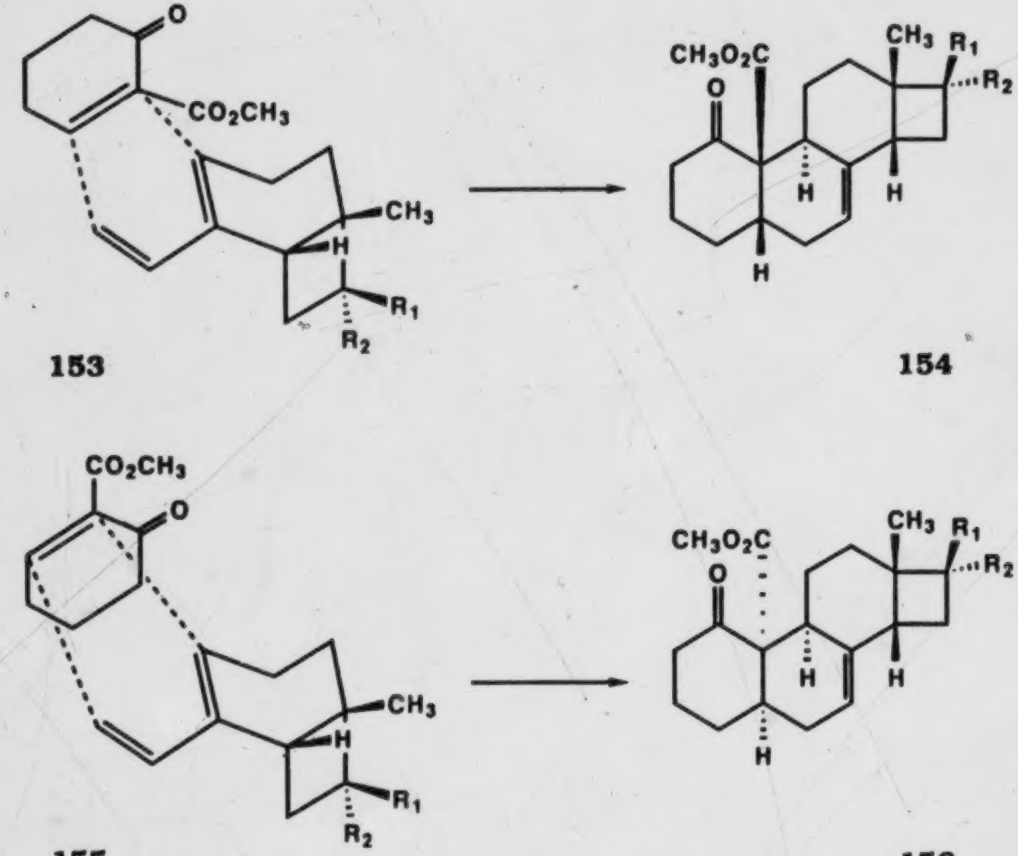
A potentially very efficient approach for the formation of the steroidal skeleton of strophanthidin would involve the Diels-Alder reaction of the enone-ester **150** with the diene **151** to give the adduct **152**.



150 **151** **[illegible]2**

This substance possesses a number of features present in the strophanthidin skeleton and could presumably be manipulated into the production of the desired target molecule.

An analysis of the Diels-Alder reaction shows that, on the basis of the general rules for this process, there are four possible transition states. The formation of the intermediates **153** and **155** involve the attack of the dienophile from the convex face of the diene molecule, to give the compounds **154** and **156**, respectively. On the other hand, the adducts **158** and **160** result from the opposite mode of attack, from the concave face, via the transition states **157** and **159**. Note that the adduct **154** is the substance that possesses the stereochemical features required for the synthesis of **135**. Studies on the Diels-Alder reactions of the enone-ester **150** have shown that the products obtained arise predominantly from the addition of the diene *endo* to the ester group of **150**.[97]



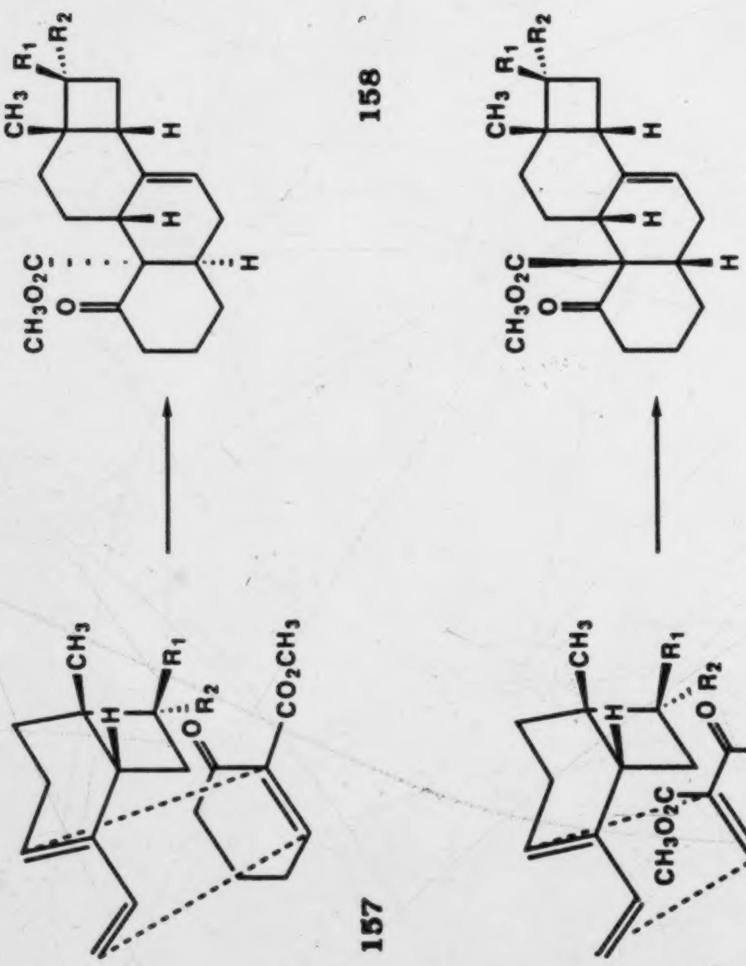
153

154

155

156

O
CO₂CH₃
CH₃
H
R₁
R₂
CH₃O₂C
O
CH₃
H


CH$_3$
R$_1$
R$_2$
CO$_2$CH$_3$
CH$_3$O$_2$C
O
H

157

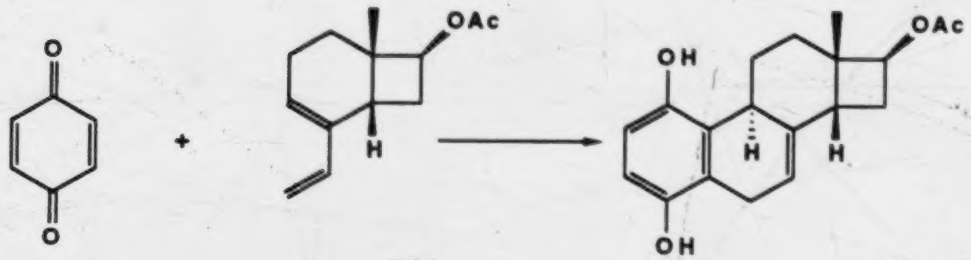
158

159

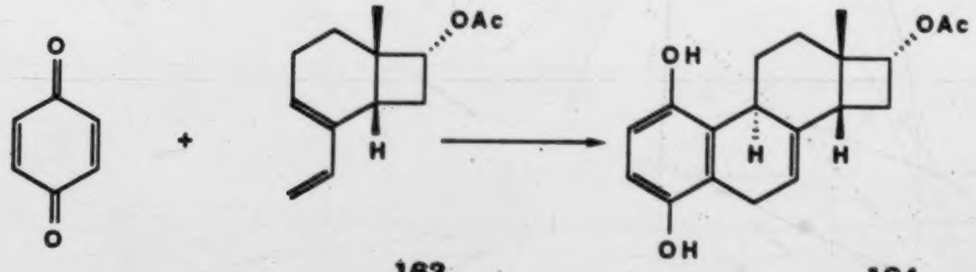
160

Therefore, it may be expected that the adducts **154** and **158** might be formed preferentially. Moreover, addition from the concave face of the diene (i.e. **158**) would involve far more steric interactions than the addition from the opposite face. This led to the prediction that the transition state **153** would be the preferred pathway for the reaction and hence, the adduct **154** the major product.

Preliminary studies carried out in our laboratories[98] have shown that the Diels-Alder reaction of the dienes **161** and **163** with benzoquinone give the adducts **162** and **164**, respectively.



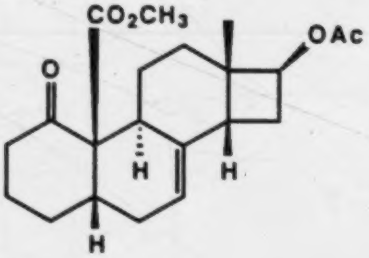
161 **162**



163 **164**

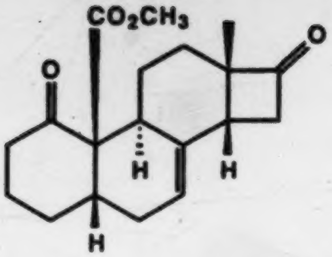
Both adducts **162** and **164** were formed by addition of benzoquinone from the less hindered convex face of the dienes. This gave the required *trans* relationships between the proton at C-9 and the angular methyl group on C-13. Moreover, the Diels-Alder reactions of the dienes **161** and **163** with the enone-ester **150** have been carried out[98] and the results are discussed below.

When the diene **161** was reacted with **150** under Lewis acid catalysis conditions, a 1:1:1 mixture of adducts was obtained. After a painstaking chromatographic separation the adduct **165** was isolated and characterized by spectroscopic means.



165

The structure of **165** was confirmed by means of an X-ray crystallographic analysis of the derivative **166**, obtained from **165** by hydrolysis of the acetyl group followed by oxidation. The production of only three of the four possible adducts allowed the ruling out of the transition state **159**, which would result from a greatly disfavored *endo*-to-ketone attack from the sterically hindered concave face of the diene.



166

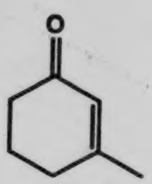
Similarly, the reaction of the enone-ester **150** with **163** gave a 1:1:0.3 mixture of adducts. Hydrolysis of the acetate and oxidation gave a mixture of ketones of the type of **166** that was spectroscopically identical, except for the proportions, to an analogous mixture obtained from **161**. The change in stereoselectivity observed in changing from **161** to **163** suggested that the *endo* orientation of the acetate group in **163** increases the steric hindrance for attack of the dienophile from the concave face, thereby favoring the addition from the convex face. It was concluded then that by increasing the steric bulk even further the facial stereoselectivity could be improved so as to completely eliminate the mediation of the transition states **157** and **159**.

The objectives of the present work are first, the duplication of the previous results and second, to test the ideas outlined above. The results of our experiments are presented in the second part of this thesis.

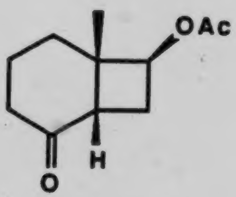
Results and Discussion

The synthesis of the dienes **161** and **163** was effected using the commercially available Douglas-fir beetle pheromone 3-methyl-2-cyclohexen-1-one (**167**) as the starting material. Irradiation of a mixture of the enone **167** and vinyl acetate in benzene with a 450 W Hanovia high-pressure mercury-vapor lamp using a pyrex filter for 50 hours gave a yellow oil that was immediately treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene for two days. Chromatographic separation of the products gave a 64% yield of the two keto-acetates **168** and **169** in a 2:1 ratio. Compound **168** displayed two carbonyl bands at 1737 and 1706 cm^{-1} in the infrared spectrum. The ^1H nmr spectrum showed a multiplet at δ 4.92 for the proton adjacent to the acetoxy group and singlets at δ 2.06 and 1.23 for the two methyl groups. Its high resolution electron impact mass spectrum did not present a molecular ion peak, but a $[M+18]^+$ peak was observed in the chemical ionization (NH_3) mass spectrum at m/z 214.30. The compound **169** was isolated as a white crystalline solid with a melting point of 53-54°C. The infrared spectrum showed carbonyl signals at 1728 and 1689 cm^{-1} for the ester and ketone carbonyl groups, respectively. The chemical ionization mass spectrum showed a $[M+18]^+$ peak at 214.27 and the ^1H nmr spectrum displayed a triplet at δ 4.72

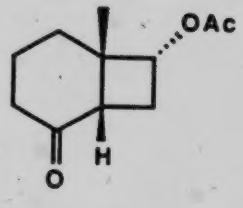
and singlets at δ 2.06 and 1.26. The relative stereochemistry of these substances was deduced by comparison of their physical and spectroscopic properties with the values reported previously.[98]



167

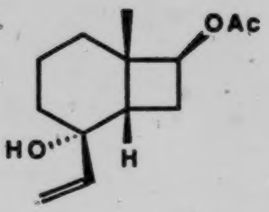


168

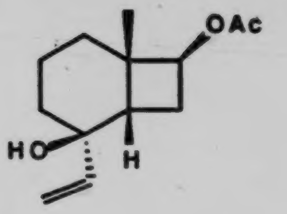


169

The keto-acetate **168** was then subjected to treatment with vinyllithium at low temperature, to give a 4:1 mixture of the epimeric unsaturated hydroxy-esters **170** and **171** in a 59% yield. The ^{1}H nmr spectrum of the mixture clearly showed two sets of signals for the two methyl groups and for the vinylic protons. Bands at 3460 and 1730 cm^{-1} in the infrared spectrum confirmed the existence of a hydroxyl and an ester carbonyl group. The mass spectrum did not display the molecular ion. Nevertheless an $[M-18]^+$ peak was observed at m/z 206.1307, corresponding to the molecular formula $C_{13}H_{18}O_2$. The stereochemistry around the carbon atom bearing the hydroxyl group was assigned on the basis of the assumption that the major product should originate from the addition of the organometallic reagent from the less hindered face of the molecule.



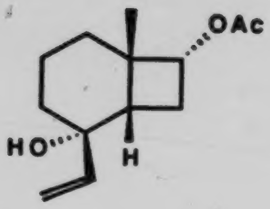
170



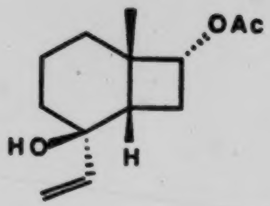
171

The diene **161** was obtained in 62% yield by treatment of the mixture of **170** and **171** with tosyl isocyanate in benzene, followed by pyrolysis of the resulting material at 120°C under vacuum. Compound **161** showed signals for the vinylic protons at δ 6.27, 5.84 and 4.90 in the ^{1}H nmr spectrum, as well as methyl groups at δ 2.05 and 1.16. Its infrared spectrum displayed bands at 1742, 1635 and 1600 cm^{-1}, confirming the presence of the ester and olefin functions. In the high resolution mass spectrum a molecular ion was discerned at m/z 206.1307, in congruence with the molecular formula $C_{13}H_{18}O_2$.

The epimeric diene **163** was prepared from **169** in an analogous manner. Treatment of **169** with vinyllithium gave a 60% yield of the unsaturated hydroxy-esters **172** and **173** in a 6:1 ratio. Dehydration of the mixture using the same methodology as before afforded the compound **163** in 70% yield.

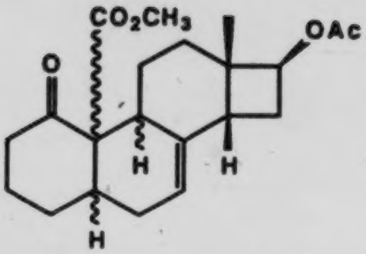


172



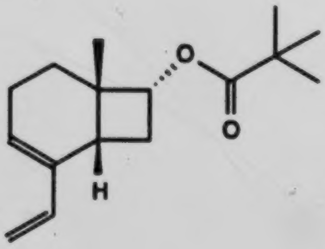
173

Having obtained the required dienes we proceeded to carry out the corresponding Diels-Alder reactions. When **161** was treated with the enone-ester **150** at -30°C in the presence of stannic chloride, a 1:1:1 mixture of adducts **174** was obtained in 62% yield. The ^{1}H nmr spectrum of this mixture revealed a multiplet at δ 5.30 with an integral of 3, for the vinylic protons; signals corresponding to the methoxy groups at δ 3.83, 3.75 and 3.72, in a 1:1:1 integral ratio; singlets at δ 2.12 and 2.07, with a total integral of 9, representing the acetates and finally, methyl peaks at δ 1.15, 1.08 and 0.99. In the infrared spectrum, bands at 1735 and 1715 cm^{-1} confirmed the presence of both the ester and ketone groups, and the mass spectrum presented a molecular ion peak at m/z 360.1933, in concordance with the formula $C_{21}H_{28}O_5$. Gas chromatography of the mixture clearly showed three peaks.



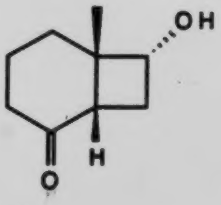
174

Being able to reproduce the results of this experiment we decided not to repeat the Diels-Alder reaction of the diene-acetate **163** but to go ahead with our plans towards the improvement of the stereoselectivity of the reaction. As was outlined before, our intention was to replace the acetate in **163** for a more sterically demanding moiety. A pivalate would meet this requirement and we set forth to synthesize the diene-ester **175**.



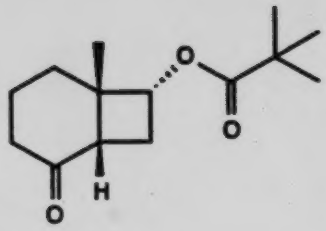
175

The replacement of the acetyl group was carried out easily in two steps. Hydrolysis of the acetate by treatment of **169** with an excess of potassium carbonate in wet methanol afforded a 92% yield of the hydroxy-ketone **176**. The infrared spectrum of this substance displayed bands at 3410 (OH) and 1700 cm^{-1} (C=O), and its mass spectrum showed a molecular ion peak at m/z 154.0992, in accordance with the molecular formula $C_9H_{14}O_2$. The ^1H nmr spectrum in deuterated methanol presented a doublet of doublets at δ 3.83 representing the proton adjacent to the hydroxyl group.



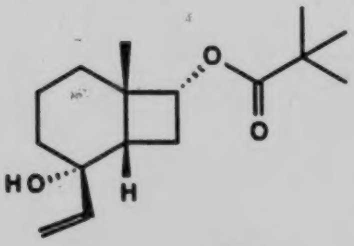
176

Treatment of **176** with an excess of pivaloyl chloride in pyridine, in the presence of a catalytic amount of 4-dimethylaminopyridine gave a 95% yield of the desired keto-ester **177**. The ^1H nmr spectrum of this substance showed a triplet at δ 4.71 for the proton at the base of the pivalate and singlets at δ 1.27 and 1.22 with integrals of 3 and 9, respectively. The infrared spectrum presented an ester carbonyl band at 1729 cm^{-1} and a ketone carbonyl at 1706 cm^{-1}. The mass spectrum did not show a molecular ion peak, but an $[M-102]^+$ peak was observed at m/z 136.0889, resulting from the loss of a pivalic acid unit.



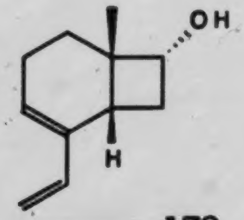
177

The next step involved the preparation of the unsaturated hydroxy-ester **178** by treatment of **177** with one equivalent of vinyllithium in tetrahydrofuran at low temperature. A single isomer was obtained in a 61% yield, as well as some unchanged starting material. The infrared spectrum of **178** displayed bands at 3480 (OH), 1730 (ester C=O) and 1695 cm^{-1} (C=C). Its mass spectrum did not show a molecular ion peak; instead, a $[M-17]^+$ peak was present at m/z 249.1853, in agreement with the formula $C_{16}H_{25}O_2$. The fact that only one isomer was obtained supported our belief that the face selectivity for the reactions of **175** would be improved with the introduction of the bulky substituent.



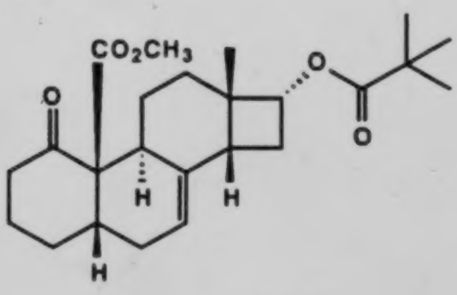
178

Unfortunately, attempts to dehydrate compound **178** to obtain **175** were doomed to failure. This should not have been totally unexpected since the α-hydroxyl group is located in the sterically very hindered concave face of the molecule. We decided then to carry out the substitution of the acetyl group after the diene moiety had been assembled. For this purpose the diene-acetate **163** was subjected to hydrolysis conditions with an excess of potassium carbonate in wet methanol, to give the hydroxy-diene **179** in 92% yield. The ^{1}H nmr of **179** displayed signals for the vinylic protons at δ 6.26, 5.80, 4.96 and 4.90, as well as a broad quartet at δ 3.96 representing the proton at the base of the hydroxyl group. Treatment of **179** with an excess of pivaloyl chloride in pyridine, in the presence of 4-dimethylaminopyridine gave the desired diene-ester **175** in quantitative yield. The existence of the pivaloyl moiety was confirmed by ^{1}H nmr, which showed a singlet with an integral of 9 at δ 1.19.

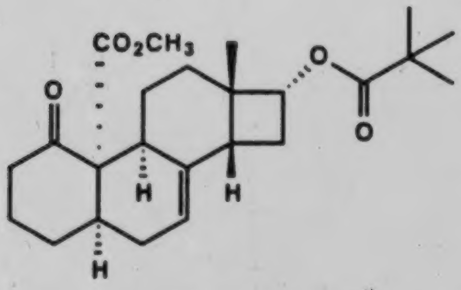


179

The Diels-Alder reaction of **175** with the enone-ester **150** proceeded smoothly in the presence of stannic chloride to give a 63% yield of a 1:1 mixture of adducts. The ^{1}H nmr spectrum of the mixture showed a multiplet at δ 5.35 for the vinylic protons, methoxy groups at δ 3.77 and 3.71, methyl groups δ 1.28 and 1.20, and t-butyl groups at δ 1.22 and 1.21. Its infrared spectrum displayed bands at 1731 and 1710 cm^{-1} for the ester and ketone carbonyls, respectively, and in the mass spectrum a molecular ion peak at m/z 402.2404 was congruous with the molecular formula $C_{24}H_{34}O_5$. On the assumption that the transition states **157** and **159** can now be ruled out, the products obtained should have the structures **180** and **181**.

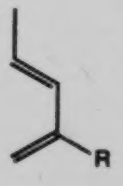


180



181

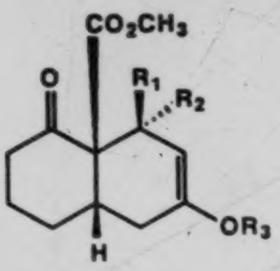
Compound **180** bears the substituents with the required stereochemistry and arose from the *endo*-to-ester attack of **150** onto **175**. The adduct **181**, on the other hand, originated from an *endo*-to-ketone delivery. We anticipate that the introduction of a bulky substituent at the 3-position of the diene moiety in **175** would influence the outcome of the reaction so as to produce **180** exclusively or with very high selectivity. The basis for this prediction rests on the results of studies carried out in our group on the Diels-Alder reactions of the enone-ester **150**.[97,99,100] It was found that the Lewis acid catalyzed Diels-Alder reaction of **150** with the 3-substituted diene **182** gave a 6:1 mixture of the adducts **184** and **185** in 66% yield.



182 R = $OPO(OEt)_2$

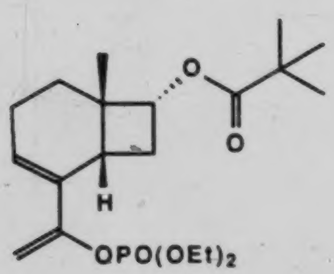
183 R = H

In contrast, when the diene **183** was used, a 5:3 mixture of the adducts **186** and **187** was obtained in only 34% yield. The next task at hand is therefore the synthesis of the diene **188**. Experiments towards the fulfillment of this goal will be carried out in our laboratories in the near future.



CO_2CH_3
O
R_1
R_2
OR_3
H

184 $R_1 = CH_3$ $R_2 = H$ $R_3 = OPO(OEt)_2$
185 $R_1 = H$ $R_2 = CH_3$ $R_3 = OPO(OEt)_2$
186 $R_1 = CH_3$ $R_2 = H$ $R_3 = H$
187 $R_1 = H$ $R_2 = CH_3$ $R_3 = H$



O
O
H
$OPO(OEt)_2$

188

Experimental.

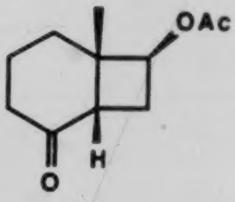
General.

For general remarks see Chapter 1 of this thesis.

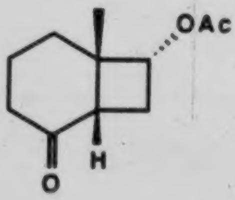
Materials.

For the methods used in the purification of solvents and other materials see Chapter 1 of this thesis.

(1R*, 6R*, 7R*)- (168) and (1R*, 6R*, 7S*)-7-acetoxy-6-methylbicyclo[4.2.0]octan-2-one (169).



168

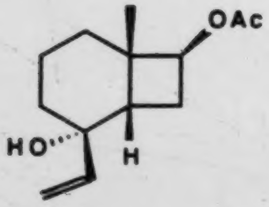


169

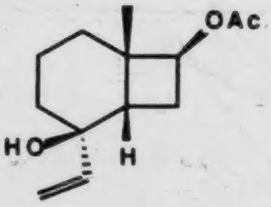
A solution of 3-methyl-2-cyclohexen-1-one (**167**) (10.7 g, 9.7 mmol) and vinyl acetate (90 mL, 84.1 g, 0.98 mol, 10.1 eq) in benzene (50 mL) was placed in a photochemical reaction vessel. The reaction mixture was cooled to 0°C and a flow of argon was passed through the solution for agitation. The solution was irradiated with a 450 W Hanovia high-pressure mercury-vapor quartz lamp using a pyrex filter. After 50 hrs. the reaction mixture was concentrated and dissolved in benzene (100 mL). 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (14.5 mL, 14.8 g, 97 mmol, 1.0 eq) was added and the mixture was refluxed for 2 days. The resulting solution was concentrated and the residue was dissolved in methylene chloride (100 mL), washed with 20% hydrochloric acid (3 × 20 mL), dried (Na_2SO_4), filtered and concentrated. Flash chromatography of the residue (20% ethyl acetate in hexane) gave the keto-acetate **168** (7.2 g, 40%) as a yellowish oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 4.92 (m, 1H, -C**H**OAc), 2.52 (m, 1H, -C**H**H-CHOAc), 2.40 (m, 3H), 2.19 (m, 1H), 2.06 (s, 3H, -OCOC**H**$_3$), 1.91 (m, 3H) 1.46 (m, 1H) and 1.23 (s, 3H, -C**H**$_3$); ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 213.9 (p), 170.5 (p), 69.8 (a), 46.6 (p), 44.6 (a), 39.9 (p), 32.9 (p), 28.6 (p), 21.3 (a), 20.9 (p); ir ($CHCl_3$ cast) 1737 (ester C=O) and 1706 cm^{-1} (ketone (C=O); ms (CI-NH_3) $[M+18]^+$ 214.30. Continued elution gave the keto-acetate **169** (4.3 g, 24%): m.p. 53-54°C (recryst. from hexane); ^{1}H nmr (400 MHz, $CDCl_3$) δ 4.72 (t, 1H, J = 8 Hz, -C**H**OAc), 2.60 (ddd, 1H, J = 7.5, J' = 9.0, J'' = 11 Hz, -C**H**H-CHOAc), 2.45 (ddd, 1H, J = 6.0, J' = 11, J'' = 17 Hz, -C**H**H-CO-), 2.32 (m, 2H), 2.18 (ddd, 1H, J = 8.5, J' = 10, J'' = 12 Hz), 2.06 (s, 3H, -OCOC**H**$_3$), 2.04 (m, 2H), 1.79 (dddd, 1H, J = 2.0, J' = 5.0, J'' = 11, J''' = 22 Hz), 1.42 (m, 1H) and 1.26 (s, 3H, -C**H**$_3$); ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 211.7 (p), 170.5 (p), 72.1 (a), 46.6 (p), 44.3

(a), 37.8 (p), 29.1 (p), 26.9 (p), 25.0 (a) and 20.1 (p); ir ($CHCl_3$ cast) 1728 (ester C=O) and 1689 cm^{-1} (ketone C=O); ms ($CI-NH_3$) $[M+18]^+$ 214.27.

(1R*, 2R*, 6R*, 7S*)- (170) and (1R*, 2R*, 6R*, 7S*)-7-acetoxy-2-vinyl-6-methylbicyclo[4.2.0]octan-2-ol (171).



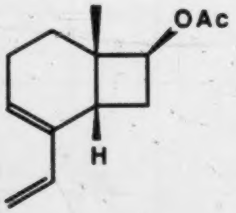
170



171

Vinyllithium (6.15 mL of a 1.65 M solution in tetrahydrofuran, 10.1 mmol, 1.0 eq) was added at -78°C to a solution of the keto-acetate **168** (1.87 g, 10.1 mmol) in tetrahydrofuran (3 mL). After stirring for 4 hrs. at -78°C, water (1 mL) was added and the resulting mixture was extracted with methylene chloride (4 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Filtration through a short column of silica gel, eluting first with hexane to remove the grease and then with 40% ethyl acetate in hexane, gave a 4:1 mixture of the unsaturated hydroxy-ketones **170** and **171** (1.34 g, 59%). The following ^1H nmr (400 MHz, $CDCl_3$) data were attributed to compound **170**: δ 5.91 (dd, 1H, J = 11, J' = 18 Hz, -**CH**=CH_2), 5.22 (br. d, 1H, J = 18 Hz, *trans* -CH=CH_2), 5.02 (br. d, 1H, J = 11 Hz, *cis* -CH=C**H**$_2$), 4.83 (dd, 1H, J = 5.0, J' = 7.0 Hz, -C**H**OAc), 2.04 (s, 3H, -OCOC**H**$_3$) and 1.03 (s, 3H, -C**H**$_3$). The following ^{1}H nmr (400 MHz, CDCl$_3$) data were attributed to compound **171**: δ 5.79 (dd, 1H, J = 11, J' = 18 Hz, -C**H**=CH$_2$), 5.19 (br. d, 1H, J = 18 Hz, *trans* -CH=C**H**$_2$), 5.07 (br. d, 1H, J = 11 Hz, *cis* -CH=C**H**$_2$), 4.73 (m, 1H, -C**H**OAc), 1.92 (s, 3H, -OCOC**H**$_3$) and 0.95 (s, 3H, -C**H**$_3$). The following spectral data were obtained on the mixture: ir (neat) 3460 (OH) and 1730 cm^{-1} (C=O); ms [M-18]$^+$ 206.1304 (calcd. for $C_{13}H_{18}O_2$: 206.1307).

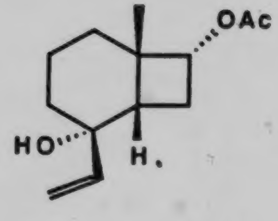
(1R*, 6R*, 7S*)-7-acetoxy-2-vinyl-6-methylbicyclo[4.2.0]oct-2-ene (161).



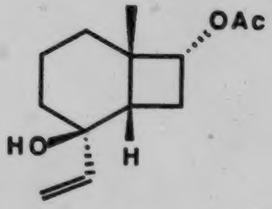
A mixture of the unsaturated hydroxy-ketones **170** and **171** (932 mg, 4.2 mmol) and tosyl isocyanate (0.62 mL, 902 mg, 4.6 mmol, 1.1 eq) in benzene (5 mL) was stirred at 0°C for 2 hrs. Water (2 mL) was then added and the resulting suspension was extracted with ether (5 × 3 mL), dried (Na$_2$SO$_4$), filtered and concentrated. Pyrolysis of the residue (120°C at *ca.* 2 torr) followed by HPMPLC (20% ethyl acetate in hexane) gave the diene-acetate **161** (530 mg, 62%): ^{1}H nmr (400 MHz, CDCl$_3$)

δ 6.27 (dd, 1H, $J = 11$, $J' = 18$ Hz, -CH=CH_2), 5.84 (dd, 1H, $J = 3.0$, $J' = 6.5$ Hz -CH=CH-CH=CH_2), 4.89 (m, 3H, CH_2= and -CHOAc), 2.49 (m, 2H), 2.36 (m, 1H), 2.24 (m, 1H), 2.03 (m, 1H), 2.05 (s, 3H, -$OCOCH_3$), 1.72 (ddd, 1H, $J = 3.0$, $J' = 6.0$, $J'' = 13$ Hz), 1.16 (s, 3H, -CH_3) and 1.14 (m, 1H); ir ($CHCl_3$ cast) 1742 (C=O), 1635 (C=C); ms M^+ 206.1305 (calcd. for $C_{13}H_{18}O_2$: 206.1307).

(1R*, 2R*, 6R*, 7R*)- (172) and (1R*, 2S*, 6R*, 7R*)-7-acetoxy-2-vinyl-6-methylbicyclo[4.2.0]octan-2-ol (173).



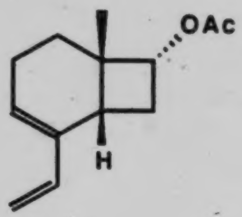
172



173

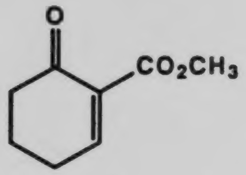
Vinyllithium (4.6 mL of 1.69 M solution in tetrahydrofuran, 7.8 mmol, 1.0 eq) was added at -78°C to a solution of the keto-acetate **169** (1.43 g, 7.8 mmol) in tetrahydrofuran (15 mL). After stirring at -78°C for 2 hrs., saturated aqueous ammonium chloride solution (5 mL) was added and the resulting suspension was extracted with methylene chloride (5 × 5 mL), dried (Na_2SO_4), filtered and concentrated. Filtration of the residue through a short column of silica gel, eluting first with hexane to remove the grease and then with 40% ethyl acetate in hexane, gave a 6:1 mixture of the unsaturated hydroxy-acetates **172** and **173** (1.05 g, 60%). The following ^{1}H nmr (400 MHz, CDCl$_3$) data were attributed to compound **172**: δ 6.04 (dd, 1H, *J* = 11, *J'* = 18 Hz, -C**H**=CH$_2$), 5.29 (br. d, 1H, *J* = 18 Hz, *trans* -CH=C**H**$_2$), 5.09 (dd, 1H, *J* = 7.0, *J'* = 9.0 Hz, *cis* -CH=C**H**$_2$), 4.56 (dd, 1H, *J* = 7.0, *J'* = 9.0 Hz, -C**H**OAc), 2.03 (s, 3H, -OCOC**H**$_3$) and 1.17 (s, 3H, -C**H**$_3$). The following ^{1}H nmr (400 MHz, CDCl$_3$) were attributed to compound **173**: δ 5.81 (dd, 1H, *J* = 11, *J'* = 17 Hz, -C**H**=CH$_2$), 5.22 (dd, 1H, *J* = 2.0, *J'* = 17 Hz, *trans* -CH=C**H**$_2$), 5.02 (dd, 1H, *J* = 2.0, *J'* = 11 Hz, *cis* -CH=C**H**$_2$), 4.51 (dd, *J* = 7.0, *J'* = 9.0 Hz -C**H**OAc), 2.06 (s, 3H, -OCOC**H**$_3$) and 1.26 (s, 3H, -OCOC**H**$_3$).

(1R*, 6R*, 7R*)-7-acetoxy-2-vinyl-6-methylbicyclo[4.2.0]oct-2-ene (163).



A mixture of the unsaturated hydroxy-acetates **172** and **173** (750 mg, 3.3 mmol) and tosyl isocyanate (0.5 mL, 725 mg, 3.7 mmol, 1.1 eq) in benzene (5 mL) was stirred at 0°C for 2 hrs. and then allowed to warm up to room temperature for 12 hrs. Water (2 mL) was added and the resulting suspension was extracted with methylene chloride (3 × 4 mL), dried (Na_2SO_4), filtered and concentrated. The residue was subjected to pyrolysis (120°C at *ca.* 1.5 torr) and the product was then purified by HPMPLC (10% ethyl acetate in hexane) to afford the diene-acetate **163** (480 mg, 70%): ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.25 (dd, 1H, *J* = 11, *J'* = 18 Hz, -C**H**=CH$_2$), 5.81 (br. t, 1H, *J* = 4.5 Hz, -C**H**=C-), 4.95 (d, 1H, *J* = 18 Hz, *trans* -CH=C**H**$_2$), 4.91, (d, 1H, *J* = 11 Hz, *cis* -CH=C**H**$_2$), 4.78 (t, 1H, *J* = 8 Hz, -C**H**OAc), 2.21-2.07 (m, 3H), 2.03 (s, 3H, -OCOC**H**$_3$), 1.90-1.73 (m, 2H), 1.36 (ddd, 1H, *J* = *J'* = 3.5, *J''* = 13 Hz) and 1.18 (s, 3H, -C**H**$_3$); ir ($CHCl_3$ cast) 1740 (C=O), 1635 (C=C) and 1600 cm^{-1} (C=C); ms M$^+$ 206.1306 (calcd. for $C_{13}H_{18}O_2$: 206.1307).

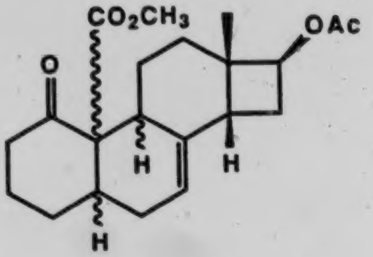
2-Carbomethoxy-2-cyclohexen-1-one (150).



Bromine (0.32 mL, 0.96 g, 6.0 mmol, 1.2 eq) was added dropwise to a solution of diphenyldiselenide (1.88 g, 6.0 mmol, 1.2 eq) in methylene chloride (5 mL). The mixture was stirred for 5 min. at room temperature and then it was cooled to 0°C. Pyridine (1.0 mL 0.98 g, 12.4 mmol, 1.24 eq) and methylene chloride (10 mL) were added and the solution was stirred for 5 more min.

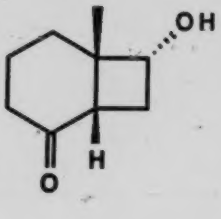
at 0°C. A solution of 2-carbomethoxycyclohexanone (1.56 g, 10 mmol) in methylene chloride (10 mL) was added dropwise. After completion of the addition, the mixture was stirred at 0°C for 30 min. and then poured over ice-cold 5% hydrochloric acid (50 mL). The organic layer was separated, washed with 5% hydrochloric acid (50 mL) and cooled to 0°C. Aqueous 30% hydrogen peroxide (4 mL) was added with stirring in two portions over a period of 10 min. and then the mixture was stirred for a further 20 min. and diluted with water. The organic layer was separated and washed with aqueous 5% sodium bicarbonate (20 mL), dried (Na_2SO_4), filtered and concentrated to give the unsaturated keto-ester **150** (1.50 g, 100%) as a yellow oil: ^1H nmr (400 MHz, $CDCl_3$) δ 7.72 (t, 1H, J = 4.0 Hz, -**CH**=) and 3.81 (s, 3H, -OCH_3); ir ($CHCl_3$ cast) 1750 (ester C=O) and 1715 (ketone C=O) and 1670 cm^{-1} (C=C); ms M^+ 154.0629 (calcd. for $C_8H_{10}O_3$: 154.0630).

The Diels-Alder reaction of 161 with 150.



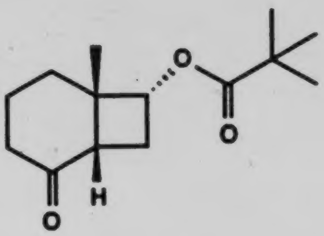
A mixture of the diene-acetate **161** (372 mg, 1.0 mmol), enone-ester **150** (560 mg, 3.6 mmol, 2.0 eq) and stannic chloride (106 μL, 235 mg, 0.9 mmol, 0.5 eq) in methylene chloride (10 mL) was stirred at -30°C for 18 hrs. The reaction mixture was then diluted with water (10 mL), the organic layer was separated and the aqueous layer was extracted with methylene chloride (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. HPMPLC of the residue (15% ethyl acetate in hexane) gave a mixture of adducts **174** (400 mg, 62%). The ^1H nmr spectrum (400 MHz, $CDCl_3$) of the mixture showed 3 sets of signals in an integral ratio of 1:1:1 and presented signals at δ 5.30 (m, 3 × 1H, -C**H**=), 4.85 (m, 2 × 1H, -C**H**OAc), 4.65 (m, 1H, -C**H**OAc), 3.83, 3.75 and 3.72 (each s, total 9H, -$CO_2C\mathbf{H}_3$), 2.12, 2.07 (each s, total 9H, -$OCOC\mathbf{H}_3$) and 1.15, 1.08 and 0.99 (each s, total 9H, -$C\mathbf{H}_3$); ir ($CHCl_3$ cast) 1735 (ester C=O) and 1715 cm^{-1} (ketone C=O); ms M^+ 360.1933 (calcd. for $C_{21}H_{28}O_5$: 360.1937).

(1R*, 6R*, 7R*)-7-hydroxy-6-methyl-2-oxobicyclo[4.2.0]octane (176).



A mixture of the keto-acetate **169** (592 mg, 3.2 mmol), and an excess of potassium carbonate in methanol (5 mL) was stirred at room temperature for 2 hrs. The solid was then filtered and thoroughly washed with methanol. Concentration of the methanolic solution followed by bulb-to-bulb distillation (90-100°C/0.6 torr) gave the hydroxy-ketone **176** (455 mg, 92%) as a clear oil: ^{1}H nmr (400 MHz, CD_3OD) δ 3.83 (dd, 1H, J = 7.0, J' = 8.0 Hz, -C**H**OH), 2.46 (m, 2H), 2.29-1.98 (m, 5H), 1.75 (m, 1H), 1.39 (m. 1H) and 1.17 (s, 3H, -C**H**$_3$); ir ($CHCl_3$ cast) 3410 (OH) and 1700 cm^{-1} (C=O); ms M$^+$ 154.0992 (calcd. for $C_9H_{14}O_2$: 154.0994).

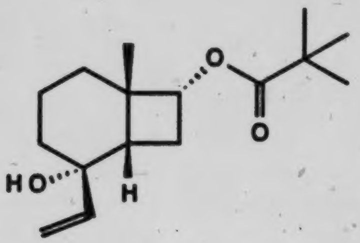
(1R*, 6R*, 7R*)-6-methyl-2-oxo-7-(1-oxo-2,2-dimethyl-1-propoxy)bicyclo[4.2.0]octane (177).



A mixture of the hydroxy-ketone **177** (365 mg, 2.4 mmol), pyridine (5 mL), pivaloyl chloride (2.05 mL, 2.01 g, 17.0 mmol, 7.0 eq) and a catalytic amount of 4-dimethylaminopyridine was stirred overnight at room temperature. The solution was then diluted with ether (20 mL), washed with 5% hydrochloric acid

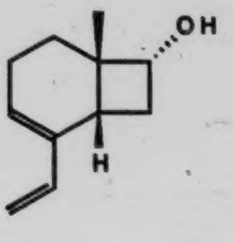
(3 × 10 mL) and saturated aqueous ammonium chloride (5 mL), dried (Na_2SO_4), filtered and concentrated. Bulb-to-bulb distillation of the residue (80-90°C/0.5 torr) gave the keto-ester **177** (530 mg, 95%): ^{1}H nmr (400 MHz, $CDCl_3$) δ 4.71 (t, 1H, *J* = 8.0 Hz, -C**H**CO-), 2.62 (ddd, 1H, *J* = 8.0, *J'* = 9.5, *J''* = 12 Hz, -C**H**H-CHO-), 2.46 (m, 1H), 2.39-2.27 (m, 2H), 2.17 (ddd, 1H, *J* = 8, *J'* = 9.5, *J''* = 12 Hz, -CH**H**-CHO-), 2.11-1.95 (m, 2H), 1.79 (m, 1H), 1.39 (m, 1H), 1.27 (s, 3H, -C**H**$_3$) and 1.22 (s, 9H, -C(C**H**$_3$)$_3$); ir ($CHCl_3$ cast) 1729 (ester C=O) and 1706 cm^{-1} (ketone C=O); ms [M-102]$^+$ 136.0889 (calcd. for $C_9H_{12}O$: 136.0889).

(1R*, 2S*, 6R*, 7R*)-2-vinyl-2-hydroxy-6-methyl-7-(1-oxo-2,2-dimethyl-1-propoxy)bicyclo[4.2.0]octane (178).



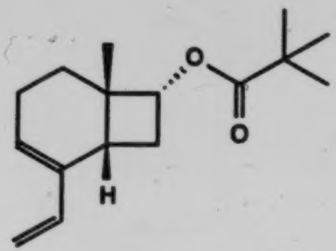
Vinyllithium (1.30 mL of a 1.65 M solution in tetrahydrofuran, 2.1 mmol, 1.0 eq) was added at -78°C to a solution of the keto-ester **177** (510 mg, 2.1 mmol) in tetrahydrofuran (4 mL). After stirring at -78°C for 90 min., the mixture was poured over saturated aqueous ammonium chloride solution (5 mL). The organic layer was separated and the aqueous phase was extracted with methylene chloride (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. HPMPLC (10% ethyl acetate in hexane) gave the starting material (60 mg, 12% recovery). Continued elution gave the unsaturated hydroxy-ester **178** (341 mg, 61% based on the consumed starting material): ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.05 (dd, 1H *J* = 11, *J'* = 17 Hz, -C**H**=CH_2), 5.30 (dd, 1H, *J* = 1.5, *J'* = 17 Hz, *trans* -CH=C**H**$_2$), 5.09 (dd, 1H, *J* = 1.5, *J'* = 11 Hz, *cis* -CH=C**H**$_2$), 4.55 (dd, 1H, *J* = 7.0, *J'* = 9.0 Hz, -C**H**CO-), 2.23 (dt, 1H, *J* = 7.5, *J'* = 11 Hz, -C**H**-CHO-), 2.01 (ddd, 1H, *J* = 9.0, *J'* = *J''* = 11 Hz, -CH**H**-CHO-), 1.87-1.68 (m, 3H),1.59 (m, 2H), 1.34 (m, 2H), 1.22 (m, 1H), 1.20 (s, 9H, -C(C**H**$_3$)$_3$) and 1.18 (s, 3H, -C**H**$_3$); ir ($CHCl_3$ cast) 3480 (OH), 1730 (C=O) and 1695 cm^{-1} (C=C); ms $[M-17]^+$ 249.1853 (calcd. for $C_{16}H_{25}O_2$: 249.1854).

(1R*, 6R*, 7R*)-2-vinyl-7-hydroxy-6-methylbicyclo[4.2.0]oct-2-ene (179).



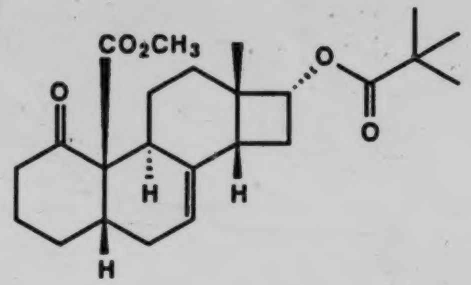
A mixture of the diene-acetate **163** (480 mg, 2.33 mmol) and an excess of potassium carbonate in methanol (5 mL) was stirred at room temperature for 2 hrs., after which the solid was filtered and washed thoroughly with methanol. Concentration of the methanolic solution followed by bulb-to-bulb distillation (90-100°C/0.5 torr) afforded the hydroxy-diene **179** (347 mg, 92%): ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.26 (dd, 1H, J = 11, J' = 18 Hz, -**C****H**=CH_2), 5.80 (br. t, 1H, J = 4.5 Hz, -C**H**=C-), 4.96 (d, 1H, J = 18 Hz, *trans* -CH=C**H**$_2$), 4.90, (d, 1H, J = 11 Hz, *cis* -CH=C**H**$_2$), 3.96 (br. q, 1H, J = 7.0 Hz, -C**H**OH), 2.65 (dt, 1H, J = 8.0, J' = 11 Hz, -C**H**-CHOH), 2.15 (m, 2H), 2.04 (br. t, 1H, J = 9.0 Hz), 1.85-1.72 (m, 2H), 1.61 (ddd, 1H, J = 9.0, J' = 10, J'' = 11 Hz, =C-C**H**H-), 1.40 (dt, 1H, J = 3.5, J' = 13 Hz, =C-CH_2-CH**H**-) and 1.12, (s, 3H, -C**H**$_3$).

(1R*, 6R*, 7R*)-2-vinyl-6-methyl-7-(1-oxo-2,2-dimethyl-1-propoxy)bicyclo[4.2.0]oct-2-ene (175).

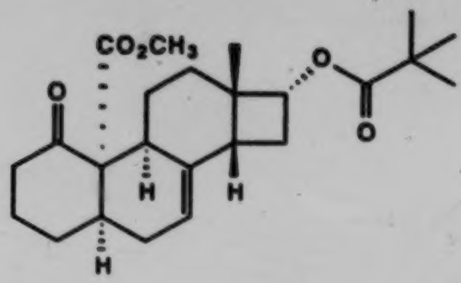


A mixture of the hydroxy-diene **179** (345 mg, 2.1 mmol) and pivaloyl chloride (2 mL, 1.96 g, 16.3 mmol, 7.8 eq) and a catalytic amount of 4-dimethylaminopyridine in pyridine (5 mL) was stirred at room temperature for 14 hrs. The solution was then diluted with ether (20 mL), washed with 5% hydrochloric acid (3 × 10 mL) and saturated aqueous ammonium chloride (5 mL), dried (Na_2SO_4), filtered and concentrated. Bulb to bulb distillation of the residue gave the diene-ester **175** (516 mg, 99%): ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.25 (dd, 1H, *J* = 11, *J'* = 18 Hz, -**C**H=CH$_2$), 5.81 (br. t, 1H, *J* = 4.5 Hz, -**C**H=C-), 4.96 (d, 1H, *J* = 18 Hz, *trans* -CH=C**H**$_2$), 4.91, (d, 1H, *J* = 11 Hz, *cis* -CH=C**H**$_2$), 4.75 (t, 1H, *J* = 8 Hz, -**C**HOCO-), 2.68 (dt, 1H, *J* = 8.0, *J'* = 11 Hz, -CHH-CHO-), 2.18 (br. t, 1H, *J* = 9.0 Hz, =C-C**H**-), 2.11 (m, 2H), 1.90-1.84 (m, 2H), 1.34 (m, 1H, =C-CH$_2$-CHH-), 1.20 (s, 3H, -C**H**$_3$) and 1.19 (s, 9H, -C(C**H**$_3$)$_3$).

A 1:1 mixture of adducts 180 and 181.



180



181

A mixture of the enone-ester **150** (640 mg, 4.2 mmol, 2.0 eq), the diene ester **175** (516 mg, 2.1 mmol) and stannic chloride (123 µL, 272 mg, 1.0 mmol, 0.5 eq) in methylene chloride (10 mL) was stirred at -30°C for 19 hrs. The reaction mixture was then diluted with water (10 mL), the organic layer was separated and the aqueous layer was extracted with methylene chloride (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. HPMPLC of the residue (10% ethyl acetate in hexane) gave a 1:1 mixture of the adducts **180** and **181** (527 mg, 63%): ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.35 (m, 2 × 1H, -C**H**=), 4.75, 4.57 (each m, each 1H, -C**H**OCO(CH_3)$_3$), 3.77, 3.71 (each s, each 3H, -OC**H**$_3$), 1.28, (s, 3H, -C**H**$_3$), 1.22, 1.21 (each s, each 9H, -C(C**H**$_3$)$_3$) and 1.20 (s, 3H, -C**H**$_3$); ir ($CHCl_3$ cast) 1731 (ester C=O) and 1710 cm^{-1} (ketone C=O); ms M$^+$ 402.2404 (calcd. for $C_{24}H_{34}O_5$: 402.2407).

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